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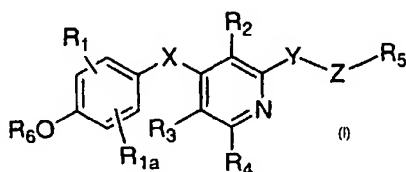
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WO 03/094845 A2

(54) Title: PYRIDINE-BASED THYROID RECEPTOR LIGANDS



(57) Abstract: Novel pyridine-based thyroid receptor ligands are provided which have the general formula (I) wherein: X is oxygen (-O-), sulfur (-S-), sulfoxide (-S(O)-), sulfonyl (-SO<sub>2</sub>-), CR<sub>8</sub>R<sub>8</sub>' or NR<sub>8</sub>; Y is -NR<sub>8</sub>, oxygen (-O-), -CH<sub>2</sub>- or sulfur (-S-); Z is a bond or substituted or unsubstituted C<sub>1-4</sub> alkyl; and wherein the substituents are as described herein. In addition, a method is provided for preventing, inhibiting or treating diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a T<sub>3</sub> regulated gene, wherein a compound as described above is administered in a therapeutically effective amount.

**PYRIDINE-BASED THYROID RECEPTOR LIGANDS****Cross-Reference to Related Application**

This application claims the benefit of U.S. Provisional Application No. 60/378,497, filed May 8, 2002,  
10 which is incorporated herein by reference in its entirety.

**Field of the Invention**

This invention relates to novel pyridine-based compounds which are thyroid receptor ligands and are  
15 preferably selective for the thyroid hormone receptor  $\beta$ . Further, the present invention relates to methods for using such compounds and to pharmaceutical compositions containing such compounds.

20                   **Background of the Invention**

While the extensive role of thyroid hormones in regulating metabolism in humans is well recognized, the discovery and development of new specific drugs for  
25 improving the treatment of hyperthyroidism and hypothyroidism has been slow. This has also limited the development of thyroid agonists and antagonists for treatment of other important clinical indications, such as hypercholesterolemia, obesity and cardiac arrhythmias.

30           Thyroid hormones affect the metabolism of virtually every cell of the body. At normal levels, these hormones maintain body weight, metabolic rate, body temperature and mood, and influence blood levels of serum low density lipoprotein (LDL). Thus, in hypothyroidism there is weight  
35 gain, high levels of LDL cholesterol, and depression. In hyperthyroidism, these hormones lead to weight loss, hypermetabolism, lowering of serum LDL levels, cardiac

5 arrhythmias, heart failure, muscle weakness, bone loss in postmenopausal women, and anxiety.

Thyroid hormones are currently used primarily as replacement therapy for patients with hypothyroidism. Therapy with L-thyroxine returns metabolic functions to  
10 normal and can easily be monitored with routine serum measurements of levels of thyroid-stimulating hormone (TSH), thyroxine (3,5,3',5'-tetraiodo-L-thyronine, or  $T_4$ ) and triiodothyronine (3,5,3'-triiodo-L-thyronine, or  $T_3$ ). However, replacement therapy, particularly in older  
15 individuals, may be restricted by certain detrimental effects from thyroid hormones.

In addition, some effects of thyroid hormones may be therapeutically useful in non-thyroid disorders if adverse effects can be minimized or eliminated. These potentially  
20 useful influences include weight reduction, lowering of serum LDL levels, amelioration of depression and stimulation of bone formation. Prior attempts to utilize thyroid hormones pharmacologically to treat these disorders have been limited by manifestations of hyperthyroidism, and in  
25 particular by cardiovascular toxicity.

Development of specific and selective thyroid hormone receptor ligands, particularly agonists of the thyroid hormone receptor could lead to specific therapies for these common disorders, while avoiding the cardiovascular and  
30 other toxicity of native thyroid hormones. Tissue-selective thyroid hormone agonists may be obtained by selective tissue uptake or extrusion, topical or local delivery, targeting to cells through other ligands attached to the agonist and targeting receptor subtypes. Thyroid hormone receptor  
35 agonists that interact selectively with the  $\beta$ -form of the thyroid hormone receptor offers an especially attractive method for avoiding cardio-toxicity.

5           Thyroid hormone receptors (TRs) are, like other  
nuclear receptors, single polypeptide chains. The various  
receptor forms appear to be products of two different genes  
 $\alpha$  and  $\beta$ . Further isoform differences are due to the fact  
that differential RNA processing results in at least two  
10 isoforms from each gene. The TR $\alpha_1$ , TR $\beta_1$  and TR $\beta_2$  isoforms  
bind thyroid hormone and act as ligand-regulated  
transcription factors. In adults, the TR $\beta_1$  isoform is the  
most prevalent form in most tissues, especially in the liver  
and muscle. The TR $\alpha_2$  isoform is prevalent in the pituitary  
15 and other parts of the central nervous system, does not bind  
thyroid hormones, and acts in many contexts as a  
transcriptional repressor. The TR $\alpha_1$  isoform is also widely  
distributed, although its levels are generally lower than  
those of the TR $\beta_1$  isoform. Whereas many mutations in the TR $\beta$   
20 gene have been found and lead to the syndrome of generalized  
resistance to thyroid hormone, mutations leading to impaired  
TR $\alpha$  function have not been found.

A growing body of data suggests that many or most  
effects of thyroid hormones on the heart, and in particular,  
25 on the heart rate and rhythm, are mediated through the  $\alpha$ -  
form of the TR $\alpha_1$  isoform, whereas most actions of the  
hormone such as on the liver, muscle and other tissues, are  
mediated more through the  $\beta$ -forms of the receptor. Thus, a  
TR $\beta$ -selective agonist might not elicit the cardiac rhythm  
30 and rate influences of the hormones, but would elicit many  
other actions of the hormones. Applicants believe that the  
 $\alpha$ -form of the receptor is primarily associated with heart  
rate function for the following reasons:

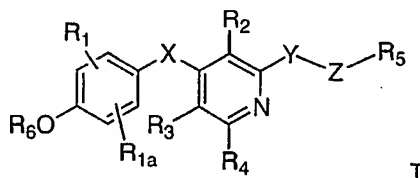
- 1) tachycardia is very common in the syndrome of  
35 generalized resistance to thyroid hormone in which  
there are defective TR $\beta$ -forms, and high  
circulating levels of T<sub>4</sub> and T<sub>3</sub>;



- 5           2) there was a tachycardia in the only described patient with a double deletion of the TR $\beta$  gene (Takeda et al, J. Clin. Endocrinol. & Metab. 1992, Vol. 74, p. 49);
- 3) a double knockout TR $\alpha$  gene (but not  $\beta$ -gene) in  
10           mice resulted in a slower mouse heart rate, as compared to control mice; and
- 4) western blot analysis of human myocardial TRs show presence of the TR $\alpha_1$ , TR $\alpha_2$  and TR $\beta_2$  proteins, but not TR $\beta_1$ .
- 15           If these indications are correct, then it may be possible that a TR $\beta$ -selective agonist could be used to mimic a number of thyroid hormone actions, while having a lesser effect on the heart. Such a compound may be used for: (1) replacement therapy in elderly subjects with hypothyroidism  
20           who are at risk for cardiovascular complications; (2) replacement therapy in elderly subjects with subclinical hypothyroidism who are at risk for cardiovascular complications; (3) obesity; (4) hypercholesterolemia due to elevations of plasma LDL levels; (5) depression; and (6)  
25           osteoporosis in combination with a bone resorption inhibitor.

### Summary of the Invention

- 30           In accordance with the illustrative embodiments and demonstrating features of the present invention, compounds are provided which are thyroid receptor ligands, and have the general formula I



35

5 wherein

X is oxygen (-O-), sulfur (-S-), sulfoxide (-S(O)-), sulfonyl (-SO<sub>2</sub>-), CR<sub>8</sub>R<sub>8</sub>' or NR<sub>8</sub>;

Y is oxygen (-O-), -NR<sub>8</sub>, -CH<sub>2</sub>- or sulfur (-S-);

Z is a bond or substituted or unsubstituted C<sub>1-4</sub> alkyl;

10 R<sub>1</sub> is halogen, trifluoromethyl, substituted or unsubstituted C<sub>1-6</sub> alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heteroaryl, substituted amide, sulfone, sulfonamide, aryloxy or C<sub>3-7</sub> cycloalkyl, wherein said aryl, heteroaryl or cycloalkyl ring(s) are attached or  
15 fused to the aromatic ring;

R<sub>1a</sub> is hydrogen, halogen, substituted or unsubstituted C<sub>1-6</sub> alkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

R<sub>2</sub> and R<sub>3</sub> are each independently hydrogen, halogen,  
20 substituted or unsubstituted C<sub>1-4</sub> alkyl or substituted or unsubstituted C<sub>3-5</sub> cycloalkyl, wherein at least one of R<sub>2</sub> and R<sub>3</sub> being other than hydrogen;

R<sub>4</sub> is hydrogen, halogen, amino, O-R<sub>7</sub>, S-R<sub>7</sub> or C<sub>1-4</sub> alkyl;

25 R<sub>5</sub> is hydroxyl (-OH), carboxylic acid (-COOH), sulfonic acid (-SO<sub>3</sub>H) or phosphonic acid (-PO<sub>3</sub>H<sub>2</sub>);

R<sub>6</sub> is hydrogen, alkyl, alkanoyl or aroyl (such as acetyl or benzoyl);

R<sub>7</sub> is hydrogen or C<sub>1-4</sub> alkyl;

30 R<sub>8</sub> for each occurrence is independently hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, aryl or substituted aryl, arylalkyl or  
35 substituted arylalkyl, alkoxy or hydroxyl; and

R<sub>8</sub>' is hydrogen, a bond, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl,

5 heterocyclo or substituted heterocyclo, aryl or substituted aryl, arylalkyl or substituted arylalkyl, alkoxy or hydroxyl, or  $R_8$  and  $R_8'$  together form a carbonyl (-CO-).

The definition of formula I above includes all prodrug-esters, stereoisomers and pharmaceutically  
10 acceptable salts of formula I.

The compounds of formula I are thyroid hormone receptor ligands and include compounds which are, for example, selective agonists, partial agonists, antagonists or partial antagonists of the thyroid receptor.

15 Preferably, the compounds of formula I possess activity as agonists of the thyroid receptor, preferably selective agonists of the thyroid receptor-beta, and may be used in the treatment of diseases or disorders associated with thyroid receptor activity. In particular, the compounds of  
20 formula I may be used in the treatment of diseases or disorders associated with metabolism dysfunction or which are dependent upon the expression of a  $T_3$  regulated gene, such as obesity, hypercholesterolemia, atherosclerosis, cardiac arrhythmias, depression, osteoporosis,  
25 hypothyroidism, goiter, thyroid cancer, glaucoma, skin disorders or diseases and congestive heart failure.

The present invention provides for compounds of formula I, pharmaceutical compositions employing such compounds and for methods of using such compounds. In  
30 particular, the present invention provides for a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I, alone or in combination with a pharmaceutically acceptable carrier.

Further, in accordance with the present invention, a  
35 method is provided for preventing, inhibiting or treating the progression or onset of diseases or disorders associated with the thyroid receptor, particularly, the thyroid receptor-beta, such as the diseases or disorders

5 defined above and hereinafter, wherein a therapeutically effective amount of a compound of formula I is administered to a mammalian, i.e., human patient in need of treatment.

The compounds of the invention can be used alone, in combination with other compounds of the present invention,  
10 or in combination with one or more other agent(s) active in the therapeutic areas described herein.

In addition, a method is provided for preventing, inhibiting or treating the diseases as defined above and hereinafter, wherein a therapeutically effective amount of  
15 a combination of a compound of formula I and another compound of the invention and/or another type of therapeutic agent, is administered to a mammalian patient in need of treatment.

Preferably, compounds of this invention include  
20 embodiments of formula I wherein

X is oxygen, sulfur, sulfoxide, sulfonyl, -CH<sub>2</sub>- or -NH-;

Y is oxygen or -NH-;

R<sub>1</sub> is halogen, substituted or unsubstituted C<sub>1-6</sub> alkyl, C<sub>3</sub>-, cycloalkyl, substituted aryl, aryloxy, substituted  
25 amide, sulfone or sulfonamide, wherein R<sub>1</sub> is attached ortho to the R<sub>6</sub>O- group;

R<sub>2</sub> and R<sub>3</sub> are each independently iodo, bromo, chloro or fluoro;

30 R<sub>4</sub> is hydrogen, fluoro, chloro, amino, -OCH<sub>3</sub>, hydroxyl (-OH) or methyl;

R<sub>5</sub> is carboxylic acid; and

R<sub>6</sub> is hydrogen.

Other preferred embodiments of the invention include  
35 compounds of formula I wherein

X is carbonyl, CHR<sub>8</sub> or NR<sub>8</sub>;

Y is oxygen or -NH-;

5  $R_1$  is halogen, substituted or unsubstituted  $C_{1-6}$  alkyl, substituted aryl, substituted amide, sulfone, sulfonamide or  $C_{3-7}$  cycloalkyl;

$R_2$  and  $R_3$  are independently bromo, chloro or methyl;

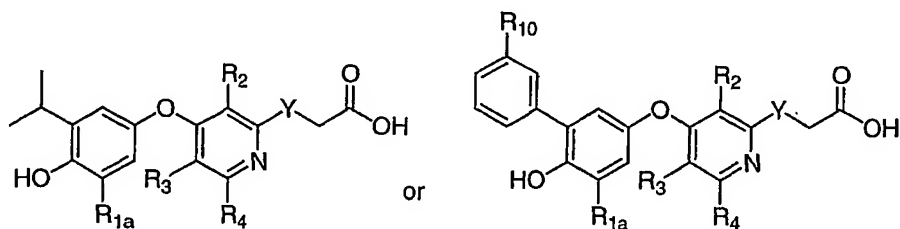
10  $R_4$  is hydrogen, fluoro, chloro, hydroxyl, amino, methoxy or methyl;

$R_5$  is a carboxylic acid; and

$R_6$  is hydrogen.

Further preferred embodiments of the invention include compounds of formula I having the structure:

15



wherein

$Y$  is oxygen or  $-NH-$ .

20  $R_{1a}$  is hydrogen, methyl or ethyl;

$R_2$  and  $R_3$  are halogen;

$R_4$  is hydrogen, halogen, amino,  $-OCH_3$ , or hydroxyl; and

$R_{10}$  is hydrogen, halogen or substituted or unsubstituted  $C_{1-4}$  alkyl.

25

### Detailed Description of the Invention

The following abbreviations have the indicated meanings:

30

Ar = aryl

Bn = benzyl

DMF = N,N-dimethylformamide

DMSO = dimethyl sulfoxide

- 5 Et = ethyl  
EtOAc = ethyl acetate  
g = gram(s)  
h or hr = hour(s)  
Me = methyl
- 10 M+H = parent plus a proton  
min = minute(s)  
mL = milliliter  
mg = milligram(s)  
mol = moles
- 15 mmol = millimole(s)  
M = molar  
Ph = phenyl  
RT = room temperature  
HPLC = high performance liquid chromatography
- 20 NMR = nuclear magnetic resonance  
THF = tetrahydrofuran  
TFA = trifluoroacetic acid  
μL = microliter

- 25 The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

- The term "thyroid receptor ligand" as used herein is intended to cover any moiety which binds to a thyroid
- 30 receptor. The ligand may act as an agonist, an antagonist, a partial agonist or a partial antagonist. Another term for "thyroid receptor ligand" is "thyromimetic".

- Unless otherwise indicated, the term "alkyl" as employed herein alone or as part of another group includes
- 35 both straight and branched chain hydrocarbons, containing 1 to 12 carbons in the normal chain, preferably 1 to 4 carbons, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, or isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-

5 dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl. "Substituted alkyl" includes an alkyl group optionally substituted with one or more functional groups which are commonly attached to such chains, such as, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heteroaryl, hydroxy, cyano, nitro, amino, halo, carboxyl or alkyl ester thereof and/or carboxamide, substituted or unsubstituted.

Unless otherwise indicated, the term "alkoxy" refers to alkyl-O-. Examples of alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like.

The term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl including 1-naphthyl and 2-naphthyl). "Substituted aryl" includes an aryl group optionally substituted through available carbon atoms with one or more groups selected from hydrogen, halo, substituted or unsubstituted alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, hydroxy, amino, nitro, cyano and/or any of the alkyl substituents set out herein.

The term "alkanoyl" refers to alkyl-C(O)-.

The term "aroyl" refers to aryl-C(O)-.

Unless otherwise indicated, the term "aryloxy" as employed herein, alone or as part of another group, denotes -OR- wherein R is aryl as defined herein.

The term "heteroaryl" means a 5- or 6-membered aromatic heterocyclic ring which contains one or more heteroatoms selected from nitrogen, sulfur, oxygen and/or a SO or SO<sub>2</sub> group. Such rings may be fused to another aryl or heteroaryl ring and include possible N-oxides. "Substituted heteroaryl" includes a heteroaryl group optionally

5 substituted with one or more substituents, such as those described for substituted alkyl and/or substituted aryl.

The term "amino" as used herein refers to  $-NR_A R_B$  where  $R_A$  and  $R_B$  are independently hydrogen, or  $R_A$  and/or  $R_B$  may optionally be a substituent, such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, cyano, nitro, carboxyl, halo, alkylthio, heteroaryl, heterocycle, heterocycle(aryl) carboalkyl and the like.

The term "substituted amide" as used herein refers to an amide linkage:  $-C(O)NR$  where  $R$  is hydrogen or may optionally be a substituent, such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, cyano, nitro, amino, carboxyl, halo, alkylthio, heteroaryl, heterocycle carboalkyl and the like.

The term "sulfonamide" as used herein refers to a sulfonamide linkage:  $-SO_2NRR'$  where  $R$  and  $R'$  are independently hydrogen, or one or both of  $R$  and  $R'$  may optionally be substituents, such as any of the substituents described in the definition of substituted alkyl or substituted amino.

25 The term "sulfone" as used herein refers to a sulfone linkage:  $-SO_2R$  where  $R$  is hydrogen or may optionally be a substituent, such as aryl, alkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, cyano, nitro, amino, carboxyl, halo, alkylthio, heteroaryl, heterocycle carboalkyl and the like.

30 The term "heterocycle" or "heterocyclo" as used herein, represents a 5- to 7-membered monocyclic ring system which may be saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from N, O or S. Exemplary monocyclic heterocyclo groups include 2- and 3-thienyl, 2- and 3-furyl, 2-, 3-, and 4-pyridyl and imidazolyl. The term heterocycle or heterocyclic ring also includes bicyclic rings wherein the five- or six-membered ring containing oxygen and/or sulfur



5 and/or nitrogen atoms as defined above is fused to a  
benzene ring and the bicyclic ring is attached by way of an  
available atom. Exemplary bicyclic heterocycle groups  
include 4-, 5-, 6- or 7-indolyl, 4-, 5-, 6-, or 7-  
isoindolyl, 5-,6-,7- or 8-quinolinyl, 5-,  
10 6-, 7- or 8-isoquinolinyl and 4-, 5-, 6- or 7-  
benzothiazoyl. "Substituted heterocyclo" includes a  
heterocyclo group optionally substituted with one or more  
substituents, such as those described for substituted alkyl  
and/or substituted aryl.

15 Unless otherwise indicated, the term "alkenyl" as  
used herein refers to straight or branched chain radicals  
of 2 to 20 carbons, preferably 2 to 12 carbons, and more  
preferably 2 to 8 carbons in the normal chain, which  
include one or more double bonds in the normal chain, such  
20 as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-  
pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-  
heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-  
dodecenyl, 4,8,12-tetradecatrienyl, and the like.  
"Substituted alkenyl" includes an alkenyl group optionally  
25 substituted with one or more substituents, such as those  
described for substituted alkyl and/or substituted aryl.

The term "arylalkyl" refers to alkyl groups as  
described above having an aryl substituent. Representative  
examples of arylalkyl include, but are not limited to,  
30 benzyl, 2-phenylethyl, 3-phenylpropyl and the like.  
"Substituted arylalkyl" includes an arylalkyl group  
optionally substituted with one or more substituents, such  
as those described for substituted alkyl and/or substituted  
aryl.

35 The term "cycloalkyl" or "cycloalkenyl" as used  
herein includes saturated or partially saturated  
(containing one or more double bonds) cyclic hydrocarbon  
groups containing 3 to 7 carbon atoms, such as cyclopropyl,

5 cyclobutyl, cyclopentyl, cyclohexyl. "Substituted cycloalkyl" or "substituted cycloalkenyl" include a cycloalkyl or cycloalkenyl group optionally substituted with one or more substituents, such as those described for substituted alkyl and/or substituted aryl.

10 The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine and iodine, with chlorine or bromine being preferred.

The  $(CH_2)_n$  group is an alkyl group that includes 0 to 15 4 carbons in the normal chain which may include 1, 2, or 3 alkyl substituents.

The term "carbonyl", as used herein, refers to a  $-C(O)-$  group.

The compounds of formula I can be present as salts, 20 which are also within the scope of this invention. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred. If the compounds of formula I have, for example, at least one basic center, they can form acid addition salts. These are 25 formed, for example, with strong inorganic acids, such as mineral acids, for example sulfuric acid, phosphoric acid or a hydrohalic acid, with strong organic carboxylic acids, such as alkanecarboxylic acids of 1 to 4 carbon atoms which are unsubstituted or substituted, for example, by halogen, 30 for example acetic acid, such as saturated or unsaturated dicarboxylic acids, for example oxalic, malonic, succinic, maleic, fumaric, phthalic or terephthalic acid, such as hydroxycarboxylic acids, for example ascorbic, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, 35 (for example aspartic or glutamic acid or lysine or arginine), or benzoic acid, or with organic sulfonic acids, such as  $(C_1-C_4)$  alkyl or arylsulfonic acids which are unsubstituted or substituted, for example by halogen, for

5 example methyl- or p-toluene- sulfonic acid. Corresponding  
acid addition salts can also be formed having, if desired,  
an additionally present basic center. The compounds of  
formula I having at least one acid group (for example COOH)  
can also form salts with bases. Suitable salts with bases  
10 are, for example, metal salts, such as alkali metal or  
alkaline earth metal salts, for example sodium, potassium or  
magnesium salts, or salts with ammonia or an organic amine,  
such as morpholine, thiomorpholine, piperidine, pyrrolidine,  
a mono, di or tri-lower alkylamine, for example ethyl,  
15 tertbutyl, diethyl, diisopropyl, triethyl, tributyl or  
dimethyl-propylamine, or a mono, di or trihydroxy lower  
alkylamine, for example mono, di or triethanolamine.  
Corresponding internal salts may furthermore be formed.  
Salts which are unsuitable for pharmaceutical uses but which  
20 can be employed, for example, for the isolation or  
purification of free compounds of formula I or their  
pharmaceutically acceptable salts, are also included.

Preferred salts of the compounds of formula I which  
contain a basic group include monohydrochloride,  
25 hydrogensulfate, methanesulfonate, phosphate or nitrate.

Preferred salts of the compounds of formula I which  
contain an acid group include sodium, potassium and  
magnesium salts and pharmaceutically acceptable organic  
amines.

30 The compounds of formula I may also have prodrug  
forms. Any compound that will be converted in vivo to  
provide the bioactive agent (i.e., the compound of formula  
I) is a prodrug within the scope and spirit of the  
invention.

35 Various forms of prodrugs are well known in the art.  
A comprehensive description of prodrugs and prodrug  
derivatives may be found in:

- 5           a.) *The Practice of Medicinal Chemistry*, Camille G. Wermuth et al., Ch 31, (Academic Press, 1996);  
          b.) *Design of Prodrugs*, edited by H. Bundgaard, (Elsevier, 1985); and  
          c.) *A Textbook of Drug Design and Development*, P. Krogsgaard-Larson and H. Bundgaard, eds. Ch 5,  
10           pgs 113 - 191 (Harwood Academic Publishers, 1991).

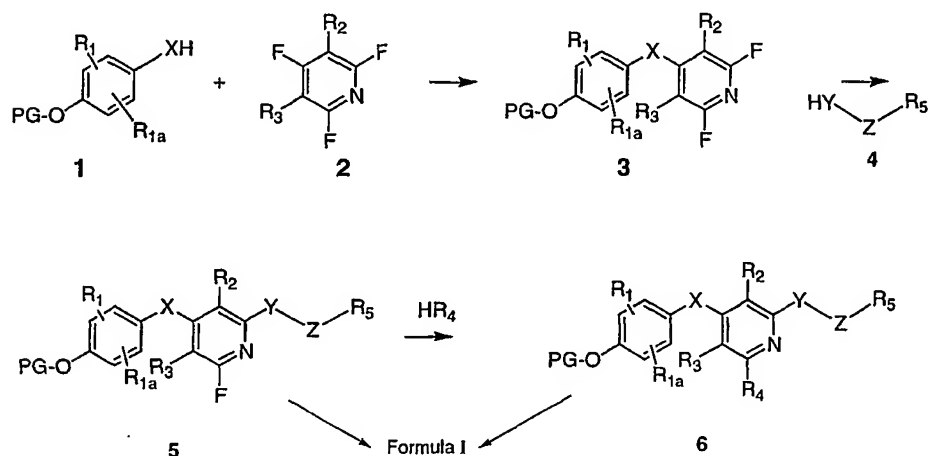
Said references are incorporated herein by reference.

Embodiments of prodrugs suitable for use in the  
15 present invention include lower alkyl esters, such as ethyl ester, or acyloxyalkyl esters such as pivaloyloxymethyl (POM).

An administration of a therapeutic agent of the invention includes administration of a therapeutically  
20 effective amount of the agent of the invention. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent to treat or prevent a condition treatable by administration of a composition of the invention. That amount is the amount sufficient to  
25 exhibit a detectable therapeutic or preventative or ameliorative effect. The effect may include, for example, treatment or prevention of the conditions listed herein. The precise effective amount for a subject will depend upon the subject's size and health, the nature and extent of the  
30 condition being treated, recommendations of the treating physician, and the therapeutics or combination of therapeutics selected for administration. Thus, it is not useful to specify an exact effective amount in advance.

The compounds of formula I of the invention can be  
35 prepared as shown in the following reaction schemes and description thereof, as well as by relevant published literature procedures that may be used by one skilled in the art. Exemplary reagents and procedures for these

5 reactions appear hereinafter and in the working Examples. Protection and deprotection in the Schemes below may be carried out by procedures generally known in the art. For example, see T. W. Greene & P. G. M. Wuts, "Protecting Groups in Organic Synthesis", 3<sup>rd</sup> Edition, (Wiley, 1999),  
 10 incorporated herein by reference.

**SCHEME 1a**

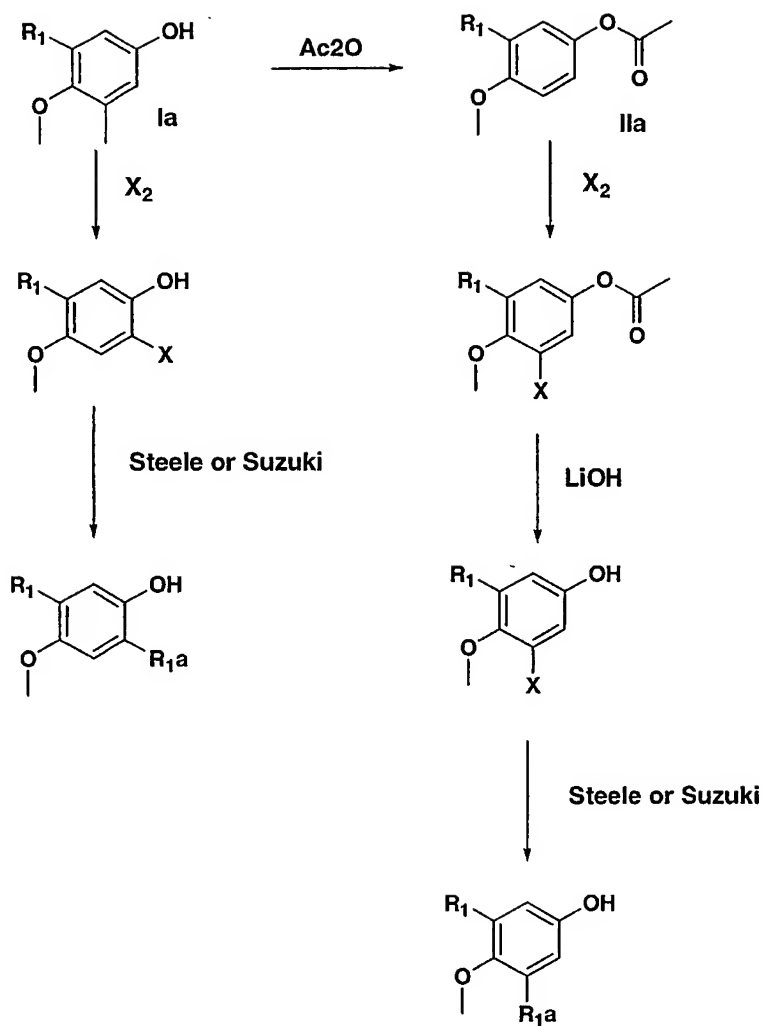
15

Scheme 1 depicts a general synthetic approach to compounds of formula I wherein  $X = O, S$  or  $NR_8$ , which utilizes the displacement reaction of an appropriately substituted phenol, thiophenol or aniline 1 such as 3-isopropyl-4-methoxyphenol or 4-methoxynaphthol with a  
 20 pentafluoropyridine 2 such as 3,5-dichloro-2,4,6-trifluoropyridine or pentafluoro pyridine to provide intermediate 3. In structure 1 and all other applicable structures contained in further schemes described below, the term "PG" refers to a protecting group appropriate for  
 25 the functional group indicated (in this instance, for a phenolic oxygen). Subsequent displacement of the 2-fluoro and 6-fluoro substituents on the pyridine 3 with nucleophiles 4 and reactant  $HR_4$  sequentially provide

5 intermediates **5** and **6** respectively. Examples of suitable nucleophiles **4** include, but are not limited to, glycine methyl ester and methyl glycolate. Examples of reactant **HR<sub>4</sub>** include, but are not limited to, alkylthiol, sodium alkoxide, alkylamine, or benzylamine. Compounds of formula  
10 I wherein X is sulfoxide or sulfonyl can be derived from intermediates **5** or **6** when X is S, via oxidation with an oxidating agent, for example mCPBA. Further protecting group and functional group manipulation of intermediates **5** or **6** will provide the compounds of formula I where X is O,  
15 S, NR<sub>8</sub>, sulfoxide and sulfonyl.

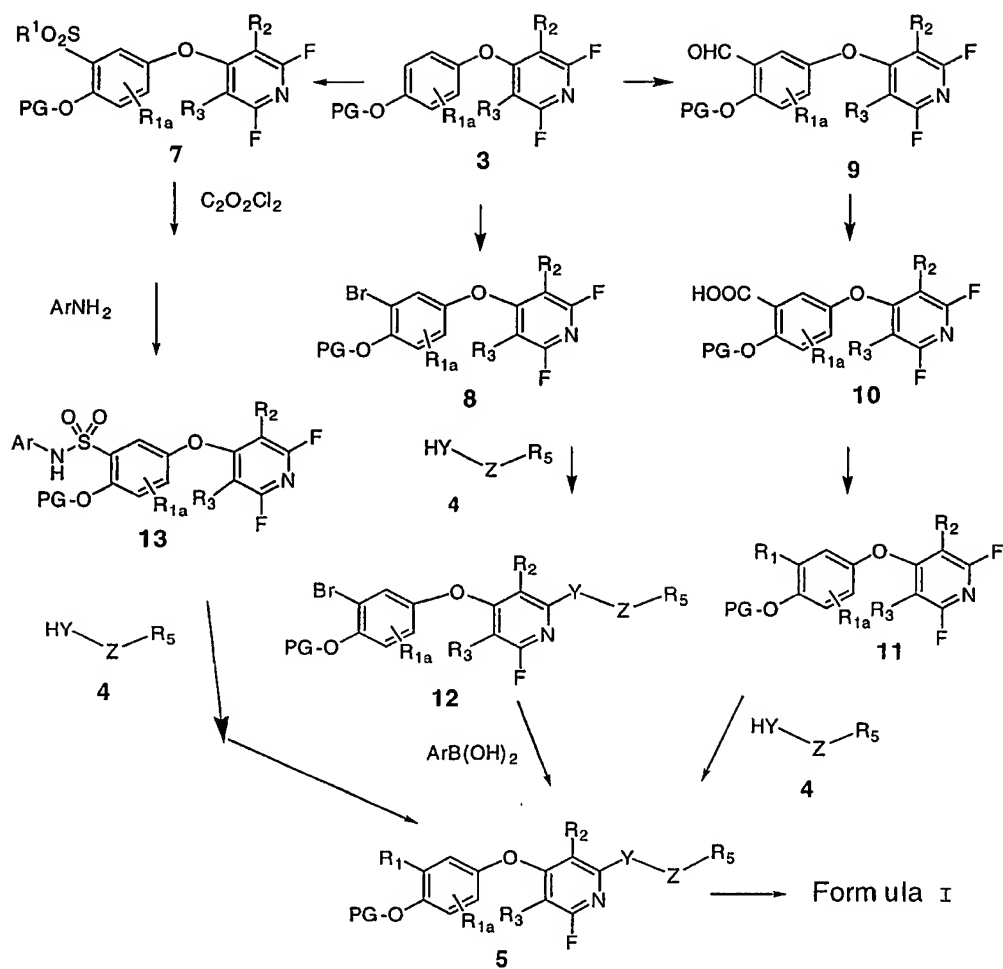
For example, where intermediate **1** is 3-isopropyl-4-methoxy phenol (X is oxygen) and intermediate **2** is 3, 5-dichloro-2, 4, 6-trifluoro pyridine (R<sub>2</sub> and R<sub>3</sub> are chlorine), the resulting intermediate **3** would be the  
20 corresponding diaryl ether where X = O and R<sub>2</sub> = R<sub>3</sub> = Cl. The 2-fluoro substituent of this intermediate can be readily displaced with nucleophile **4** where Y is O, NR<sub>8</sub>, CH<sub>2</sub> or sulfur, such as an amine or alkoxide, to form intermediate **5**. The 6-fluoro substituent of the resulting  
25 amino or alkoxy pyridine **5** can then be further displaced with a third nucleophile, such as ethylthiol in presence of potassium carbonate to provide the intermediate **6**. Deprotection or Raney-Nickel desulfurization of **5** and/or **6** would provide the desired compounds of formula I wherein R<sub>4</sub>  
30 = F or H.

Poly-substituted prime rings may be prepared by using commercially available polysubstituted phenols as illustrated below in Scheme 1b where X represents a halogen.  
35

5 **SCHEME 1b**

Alternatively, poly-substitutions can be achieved by  
 10 halogenation of intermediate Ia or its acyl derivative, intermediate IIa, followed by hydrolysis. Conversion of the halogens ( $X$ ) to an alkyl, aryl or heteroaryl may be achieved by subsequent Steele or Suzuki coupling reactions with tetraalkyltin or aryl boronic acid reagents.

5

**SCHEMES 2a & 2b****SCHEME 2a**

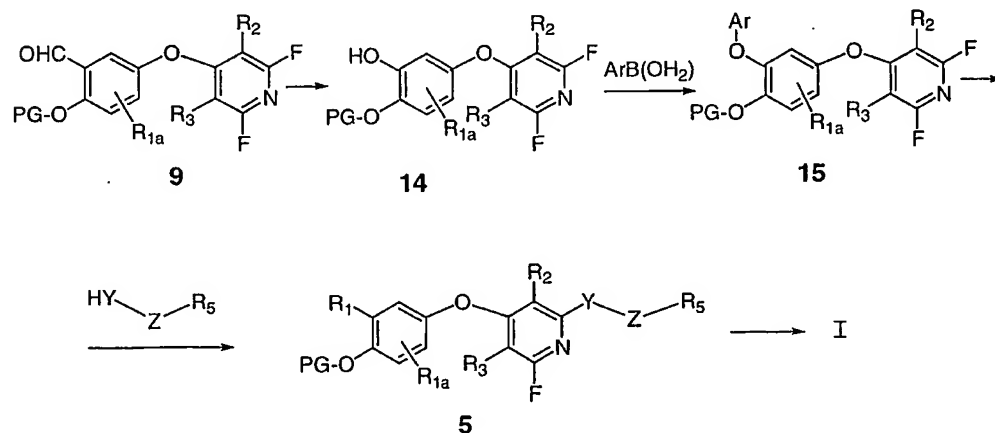
10

Scheme 2 depicts another general synthetic approach to produce the compounds of formula I wherein  $X = O$  in which the position adjacent (ortho) to  $O-PG$  ( $R_1 = H$ ) can be functionalized via sulfonation/sulfonylation, bromination or formylation to provide intermediate 7, 8 and 9. Conversion of CHO to COOH and to N-substituted amide may be carried out



5 by methods well known in the art, such as oxidation of the  
 formyl group of intermediate **9** to form intermediate **10**.  
 Carbodiimide promoted coupling of an amine with the  
 resulting carboxylic acid of intermediate **10** provides  
 intermediate **11** wherein  $R_1$  = an amide. Subsequent  
 10 displacement of the 2-fluoro substituent of **11** with an amine  
 or alkoxide **4**, where  $Y = NH$  or  $O$ , as described in the  
 description of Scheme 1, provides intermediate **5**.  
 Displacement of the 2-fluoro substituent of **8** with **4**  
 provides **12**. Subsequent Suzuki coupling of the aryl bromide  
 15 **12** with substituted phenylboronic acid provides **5** wherein  $R_1$   
 = Aryl.

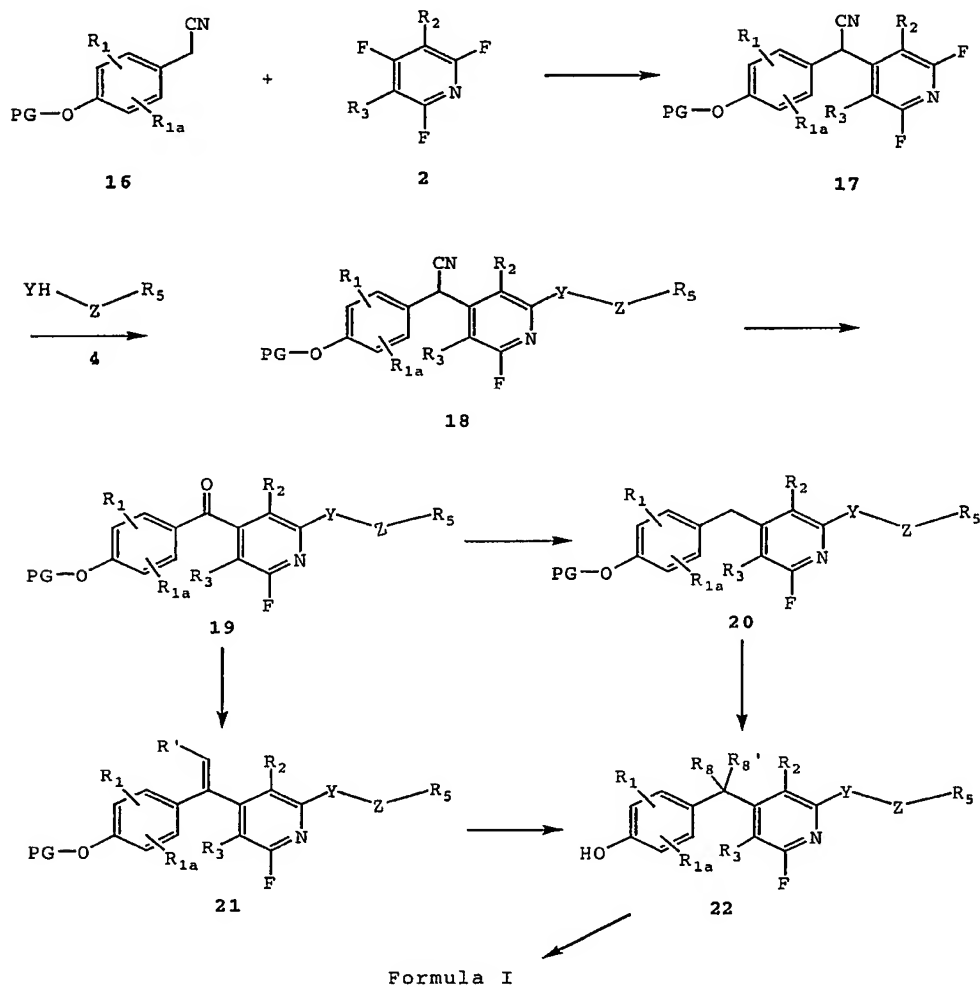
Chloronation of the aryl sulfonic acid **7** wherein  
 $R^1 = OH$ , followed by addition of an amine or aniline  
 provides the aryl sulfonamide intermediate **13**. Displacement  
 20 of the 2 fluoro substituent of **13** or **7** wherein  $R^1 = Ar$ , with  
**4** provides **5** wherein  $R_1$  = sulfonamide or sulfone.

**SCHEME 2b**

25

Scheme 2b depicts Baeyer-Villiger oxidation of the  
 intermediate **9** followed by hydrolysis provides **14**.  
 Treatment of **14** with aryl boronic acids under Evan's  
 30 conditions (see D. A. Evans et al., Tetrahedron Lett., 39,

2937-2940, 1998) provides intermediate **15**. Subsequent displacement of the 2-fluoro substituent of **15** with **4** provides **5** wherein  $R_1$  = aryloxy. Further protecting group and functional group manipulation of the intermediate **5** will provide the desired compounds of formula I where X is oxygen.

**SCHEME 3**

5           Alternatively, compounds of formula I in which X is  $\text{CR}_2\text{R}_2'$  or CO may be prepared as shown in Scheme 3. Conversion of **2** to **18** may be achieved via displacement of the 4-fluoro substituent of **2** with **16** followed by displacement of the 2-fluoro substituent of **17** with  
10   nucleophile **4**. Oxidation of **18** provides **19**. Deprotection and functional group manipulation of **19** provides compounds of formula I wherein X is CO. Alternatively, reductive deoxygenation of **19** affords **20**. Deprotection of **20** provides intermediate **22**. Alternatively, Wittig olefination of **19**  
15   provides intermediate **21**. Hydrogenation, deprotection and functional group manipulation of **21** provides intermediate **22**. Deprotection and functional group manipulation of **22** provides compounds of formula I where X is  $\text{CR}_2\text{R}_2'$ .

20           Further methods applicable to the synthesis of compounds of formula I in which X = O and  $\text{R}_2$  and  $\text{R}_3$  are independently varied as hydrogen, halogen and alkyl are described in Li et al., WO 99/00353.

25           All stereoisomers of the compounds of the instant invention are contemplated, either in admixture or in pure or substantially pure form. The compounds of the present invention can have asymmetric centers at any of the carbon atoms including any one of the R substituents. Consequently, compounds of formula I can exist in enantiomeric or diastereomeric forms or in mixtures thereof.  
30   The processes for preparation can utilize racemates, enantiomers or diastereomers as starting materials. When diastereomeric or enantiomeric products are prepared, they can be separated by conventional methods. For example, chromatographic or fractional crystallization.

35

5 UTILITIES & COMBINATIONS

## A. UTILITIES

The compounds of the present invention are thyroid  
10 receptor ligands, and include compounds which are, for  
example, selective agonists, partial agonists, antagonists  
or partial antagonists of the thyroid receptor. Preferably  
compounds of the present invention possess activity as  
agonists of the thyroid receptor, preferably selective  
15 agonists of the thyroid receptor-beta, and may be used in  
the treatment of diseases or disorders associated with  
thyroid receptor activity. In particular, compounds of the  
present invention may be used in the treatment of diseases  
or disorders associated with metabolism dysfunction or  
20 which are dependent upon the expression of a T<sub>3</sub> regulated  
gene.

Accordingly, the compounds of the present invention  
can be administered to mammals, preferably humans, for the  
25 treatment of a variety of conditions and disorders,  
including, but not limited to hypothyroidism; subclinical  
hyperthyroidism; non-toxic goiter; atherosclerosis; thyroid  
hormone replacement therapy (e.g., in the elderly);  
malignant tumor cells containing the thyroid receptor;  
30 papillary or follicular cancer; maintenance of muscle  
strength and function (e.g., in the elderly); reversal or  
prevention of frailty or age-related functional decline  
("ARFD") in the elderly (e.g., sarcopenia); treatment of  
catabolic side effects of glucocorticoids; prevention  
35 and/or treatment of reduced bone mass, density or growth  
(e.g., osteoporosis and osteopenia); treatment of chronic  
fatigue syndrome (CFS); accelerating healing of complicated  
fractures, e.g. distraction osteogenesis; in joint

5 replacement; eating disorders (e.g., anorexia); treatment  
of obesity and growth retardation associated with obesity;  
treatment of depression, nervousness, irritability and  
stress; treatment of reduced mental energy and low self-  
esteem (e.g., motivation/assertiveness); improvement of  
10 cognitive function (e.g., the treatment of dementia,  
including Alzheimer's disease and short term memory loss);  
treatment of catabolism in connection with pulmonary  
dysfunction and ventilator dependency; treatment of cardiac  
dysfunction (e.g., associated with valvular disease,  
15 myocardial infarction, cardiac hypertrophy or congestive  
heart failure); lowering blood pressure; protection against  
ventricular dysfunction or prevention of reperfusion  
events; treatment of hyperinsulinemia; stimulation of  
osteoblasts, bone remodeling and cartilage growth;  
20 regulation of food intake; treatment of insulin resistance,  
including NIDDM, in mammals (e.g., humans); treatment of  
insulin resistance in the heart; treatment of congestive  
heart failure; treatment of musculoskeletal impairment  
(e.g., in the elderly); improvement of the overall  
25 pulmonary function; skin disorders or diseases, such as  
glucocorticoid induced dermal atrophy, including  
restoration of dermal atrophy induced by topical  
glucocorticoids, and the prevention of dermal atrophy  
induced by topical glucocorticoids (such as the  
30 simultaneous treatment with topical glucocorticoid or a  
pharmacological product including both glucocorticoid and a  
compound of the invention), the restoration/prevention of  
dermal atrophy induced by systemic treatment with  
glucocorticoids, restoration/prevention of atrophy in the  
35 respiratory system induced by local treatment with  
glucocorticoids, UV-induced dermal atrophy, dermal atrophy  
induced by aging (wrinkles, etc.), wound healing, keloids,  
stria, cellulite, roughened skin, actinic skin damage,

5 lichen planus, ichthyosis, acne, psoriasis, Dernier's  
disease, eczema, atopic dermatitis, chloracne, pityriasis  
and skin scarring.

The term treatment is also intended to include  
prophylactic treatment.

10

In addition, the conditions, diseases, and maladies  
collectively referenced to as "Syndrome X" or Metabolic  
Syndrome as detailed in Johannsson *J. Clin. Endocrinol.*  
*Metab.*, 82, 727-34 (1997), may be treated employing the  
15 compounds of the invention.

#### B. COMBINATIONS

The present invention includes within its scope  
20 pharmaceutical compositions comprising, as an active  
ingredient, a therapeutically effective amount of at least  
one of the compounds of formula I, alone or in combination  
with a pharmaceutical carrier or diluent. Optionally,  
compounds of the present invention can be used alone, in  
25 combination with other compounds of the invention, or in  
combination with one or more other therapeutic agent(s),  
e.g., an antidiabetic agent or other pharmaceutically  
active material.

The compounds of the present invention may be employed  
30 in combination with other modulators and/or ligands of the  
thyroid receptor or other suitable therapeutic agents  
useful in the treatment of the aforementioned disorders  
including: anti-diabetic agents; anti-osteoporosis agents;  
anti-obesity agents; growth promoting agents (including  
35 growth hormone secretagogues); anti-inflammatory agents;  
anti-anxiety agents; anti-depressants; anti-hypertensive  
agents; cardiac glycosides; cholesterol/lipid lowering  
agents; appetite suppressants; bone resorption inhibitors;

5 thyroid mimetics (including other thyroid receptor agonists); anabolic agents; and anti-tumor agents.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g., metformin or phenformin),  
10 glucosidase inhibitors (e.g., acarbose or miglitol), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide, gliclazide, chlorpropamide and glipizide), biguanide/glyburide  
15 combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2),  
20 glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH fragment,  
25 raloxifene, calcitonin, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM) and AP-1 inhibitors.

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention  
30 include aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and  
35 5,488,064, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), a serotonin (and dopamine) reuptake inhibitor, such as sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), other thyroid receptor beta drugs,

5 such as a thyroid receptor ligand as disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), and/or an anorectic agent, such as dexamphetamine, phentermine, phenylpropanolamine or mazindol.

10 The compounds of the present invention may be combined with growth promoting agents, such as, but not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds  
15 disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

The compounds of the invention may also be used in combination with growth hormone secretagogues such as GHRP-6, GHRP-1 (as described in U.S. Patent No. 4,411,890 and  
20 publications WO 89/07110 and WO 89/07111), GHRP-2 (as described in WO 93/04081), NN703 (Novo Nordisk), LY444711 (Lilly), MK-677 (Merck), CP424391 (Pfizer) and B-HT920, or with growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including  
25 IGF-1 and IGF-2, or with alpha-adrenergic agonists, such as clonidine or serotonin 5-HT<sub>2</sub> agonists, such as sumatriptan, or agents which inhibit somatostatin or its release, such as physostigmine and pyridostigmine. A still further use of the disclosed compounds of the invention is in  
30 combination with parathyroid hormone, PTH(1-34) or bisphosphonates, such as MK-217 (alendronate).

A still further use of the compounds of the invention is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or  
35 raloxifene, or other androgen receptor modulators, such as those disclosed in Edwards, J. P. et al., *Bio. Med. Chem. Let.*, 9, 1003-1008 (1999) and Hamann, L. G. et al., *J. Med. Chem.*, 42, 210-212 (1999).



5           A further use of the compounds of this invention is in combination with steroidal or non-steroidal progesterone receptor agonists ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA).

          Examples of suitable anti-inflammatory agents for use  
10 in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel®, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen®, Celebrex®, Vioxx®), CTLA4-Ig  
15 agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®), integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab,  
20 OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome  
25 (e.g., Zelman® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

          Example of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and  
30 hydroxyzine pamoate.

          Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

35           For the treatment of skin disorders or diseases as described above, the compounds of the present invention may be used alone or optionally in combination with a retinoid, such as tretinoin, or a vitamin D analog.

5           Examples of suitable anti-hypertensive agents for use  
in combination with the compounds of the present invention  
include beta adrenergic blockers, calcium channel blockers  
(L-type and T-type; e.g. diltiazem, verapamil, nifedipine,  
amlodipine and mybefradil), diuretics (e.g.,  
10 chlorothiazide, hydrochlorothiazide, flumethiazide,  
hydroflumethiazide, bendroflumethiazide,  
methylchlorothiazide, trichloromethiazide, polythiazide,  
benzthiazide, ethacrynic acid tricrynafene, chlorthalidone,  
furosemide, musolimine, bumetanide, triamtrenene,  
15 amiloride, spironolactone), renin inhibitors, ACE  
inhibitors (e.g., captopril, zofenopril, fosinopril,  
enalapril, ceranopril, cilazapril, delapril, pentopril,  
quinapril, ramipril, lisinopril), AT-1 receptor antagonists  
(e.g., losartan, irbesartan, valsartan), ET receptor  
20 antagonists (e.g., sitaxsentan, atrisentan and compounds  
disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265),  
Dual ET/AII antagonist (e.g., compounds disclosed in WO  
00/01389), neutral endopeptidase (NEP) inhibitors,  
vasopeptidase inhibitors (dual NEP-ACE inhibitors) (e.g.,  
25 omapatrilat and gemopatrilat), and nitrates.

Examples of suitable cardiac glycosides for use in  
combination with the compounds of the present invention  
include digitalis and ouabain.

Examples of suitable cholesterol/lipid lowering agents  
30 for use in combination with the compounds of the present  
invention include HMG-CoA reductase inhibitors, squalene  
synthetase inhibitors, fibrates, bile acid sequestrants,  
ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors,  
an ileal Na<sup>+</sup>/bile acid cotransporter inhibitor, cholesterol  
35 absorption inhibitors, and cholesterol ester transfer  
protein inhibitors (e.g., CP-529414).

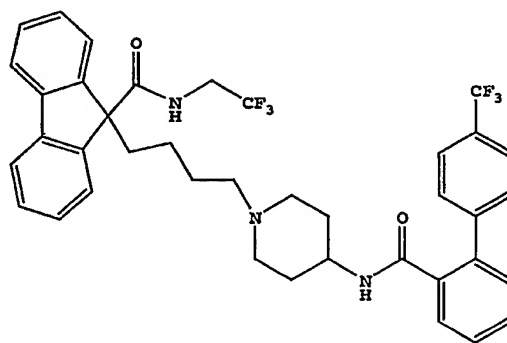
MTP inhibitors which may be employed herein in  
combination with one or more compounds of formula I include

5 MTP inhibitors as disclosed in U.S. Patent No. 5,595,872, U.S. Patent No. 5,739,135, U.S. Patent No. 5,712,279, U.S. Patent No. 5,760,246, U.S. Patent No. 5,827,875, U.S. Patent No. 5,885,983 and U.S. Patent No. 5,962,440 all incorporated herein by reference.

10 A preferred MTP inhibitor is

9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl] butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

15



The HMG CoA reductase inhibitors which may be employed in combination with one or more compounds of formula I include mevastatin and related compounds as disclosed in U.S. Patent No. 3,983,140, lovastatin (mevinolin) and related compounds as disclosed in U.S. Patent No. 4,231,938, pravastatin and related compounds such as disclosed in U.S. Patent No. 4,346,227, simvastatin and related compounds as disclosed in U.S. Patent Nos. 4,448,784 and 4,450,171. Further HMG CoA reductase inhibitors which may be employed herein include fluvastatin, disclosed in U.S. Patent No. 5,354,772, cerivastatin disclosed in U.S. Patent Nos. 5,006,530 and 5,177,080, atorvastatin disclosed in U.S. Patent Nos. 4,681,893, 5,273,995, 5,385,929 and 5,686,104, pyrazole

5 analogs of mevalonolactone derivatives as disclosed in U.S. Patent No. 4,613,610, indene analogs of mevalonolactone derivatives, as disclosed in PCT application WO 86/03488, 6-[2-(substituted-pyrrol-1-yl)-alkyl]pyran-2-ones and derivatives thereof, as disclosed in U.S. Patent No. 10 4,647,576, Searle's SC-45355 (a 3-substituted pentanedioic acid derivative) dichloroacetate, imidazole analogs of mevalonolactone, as disclosed in PCT application WO 86/07054, 3-carboxy-2-hydroxy-propane-phosphonic acid derivatives, as disclosed in French Patent No. 2,596,393, 15 2,3-disubstituted pyrrole, furan and thiophene derivatives, as disclosed in European Patent Application No. 0221025, naphthyl analogs of mevalonolactone, as disclosed in U.S. Patent No. 4,686,237, octahydronaphthalenes, such as disclosed in U.S. Patent No. 4,499,289, keto analogs of 20 mevinolin (lovastatin), as disclosed in European Patent Application No. 0,142,146 A2, as well as other known HMG CoA reductase inhibitors.

The squalene synthetase inhibitors which may be used in combination with the compounds of the present invention 25 include, but are not limited to,  $\alpha$ -phosphono-sulfonates disclosed in U.S. Patent No. 5,712,396, those disclosed by Biller et al, J. Med. Chem., 1988, Vol. 31, No. 10, pp 1869-1871, including isoprenoid (phosphinylmethyl)phosphonates, terpenoid pyrophosphates 30 disclosed by P. Ortiz de Montellano et al, J. Med. Chem., 1977, 20, 243-249, the farnesyl diphosphate analog A and presqualene pyrophosphate (PSQ-PP) analogs as disclosed by Corey and Volante, J. Am. Chem. Soc., 1976, 98, 1291-1293, phosphinylphosphonates reported by McClard, R.W. et al, 35 J.A.C.S., 1987, 109, 5544 and cyclopropanes reported by Capson, T.L., PhD dissertation, June, 1987, Dept. Med. Chem. U of Utah, Abstract, Table of Contents, pp 16, 17, 40-43, 48-51, as well as other squalene synthetase

5 inhibitors as disclosed in U.S. Patent No. 4,871,721 and  
4,924,024 and in Biller, S.A., Neuenschwander, K.,  
Ponpipom, M.M., and Poulter, C.D., Current Pharmaceutical  
Design, 2, 1-40 (1996).

Bile acid sequestrants which may be used in  
10 combination with the compounds of the present invention  
include cholestyramine, colestipol and DEAE-Sephadex  
(Secholex®, Policexide®), as well as lipostabil (Rhone-  
Poulenc), Eisai E-5050 (an N-substituted ethanolamine  
derivative), imanixil (HOE-402), tetrahydrolipstatin (THL),  
15 istigmastanylphosphorylcholine (SPC, Roche),  
aminocyclodextrin (Tanabe Seiyoku), Ajinomoto AJ-814  
(azulene derivative), melinamide (Sumitomo), Sandoz 58-035,  
American Cyanamid CL-277,082 and CL-283,546 (disubstituted  
urea derivatives), nicotinic acid, acipimox, acifran,  
20 neomycin, p-aminosalicylic acid, aspirin,  
poly(diallylmethylamine) derivatives such as disclosed in  
U.S. Patent No. 4,759,923, quaternary amine  
poly(diallyldimethylammonium chloride) and ionenes such as  
disclosed in U.S. Patent No. 4,027,009, and other known  
25 serum cholesterol lowering agents.

ACAT inhibitors suitable for use in combination with  
compounds of the invention include ACAT inhibitors as  
described in, Drugs of the Future 24, 9-15 (1999),  
(Avasimibe); "The ACAT inhibitor, Cl-1011 is effective in  
30 the prevention and regression of aortic fatty streak area  
in hamsters", Nicolosi et al, Atherosclerosis (Shannon,  
Irel). (1998), 137(1), 77-85; "The pharmacological profile  
of FCE 27677: a novel ACAT inhibitor with potent  
hypolipidemic activity mediated by selective suppression of  
35 the hepatic secretion of ApoB100-containing lipoprotein",  
Ghiselli, Giancarlo, Cardiovasc. Drug Rev. (1998), 16(1),  
16-30; "RP 73163: a bioavailable alkylsulfinyl-  
diphenylimidazole ACAT inhibitor", Smith, C., et al,

- 5 Bioorg. Med. Chem. Lett. (1996), 6(1), 47-50; "ACAT inhibitors: physiologic mechanisms for hypolipidemic and anti-atherosclerotic activities in experimental animals", Krause et al, Editor(s): Ruffolo, Robert R., Jr.; Hollinger, Mannfred A., Inflammation: Mediators Pathways  
10 (1995), 173-98, Publisher: CRC, Boca Raton, Fla.; "ACAT inhibitors: potential anti-atherosclerotic agents", Sliskovic et al, Curr. Med. Chem. (1994), 1(3), 204-25; "Inhibitors of acyl-CoA:cholesterol O-acyl transferase (ACAT) as hypocholesterolemic agents. 6. The first water-  
15 soluble ACAT inhibitor with lipid-regulating activity. Inhibitors of acyl-CoA:cholesterol acyltransferase (ACAT). 7. Development of a series of substituted N-phenyl-N'-[(1-phenylcyclopentyl)methyl]ureas with enhanced hypocholesterolemic activity", Stout et al, Chemtracts:  
20 Org. Chem. (1995), 8(6), 359-62.

Examples of suitable cholesterol absorption inhibitor for use in combination with the compounds of the invention include SCH48461 (Schering-Plough), as well as those disclosed in Atherosclerosis 115, 45-63 (1995) and J. Med.  
25 Chem. 41, 973 (1998).

Examples of suitable ileal Na<sup>+</sup>/bile acid cotransporter inhibitors for use in combination with the compounds of the invention include compounds as disclosed in Drugs of the Future, 24, 425-430 (1999).

30 Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in  
35 combination with the compounds of the present invention include testosterone, TRH diethylstilbesterol, estrogens,  $\beta$ -agonists, theophylline, anabolic steroids, dehydroepiandrosterone, enkephalins, E-series

5 prostagladins, retinoic acid and compounds as disclosed in  
U.S. Pat. No. 3,239,345, e.g., Zeranol®; U.S. Patent No.  
4,036,979, e.g., Sulbenox® or peptides as disclosed in U.S.  
Pat. No. 4,411,890.

The aforementioned patents and patent applications are  
10 incorporated herein by reference.

The above other therapeutic agents, when employed in  
combination with the compounds of the present invention,  
may be used, for example, in those amounts indicated in the  
Physicians' Desk Reference (PDR) or as otherwise determined  
15 by one of ordinary skill in the art.

Where the compounds of the invention are utilized in  
combination with one or more other therapeutic agent(s),  
either concurrently or sequentially, the following  
combination ratios and dosage ranges are preferred:

20 When combined with a hypolipidemic agent, an  
antidepressant, a bone resorption inhibitor and/or an  
appetite suppressant, the compounds of formula I may be  
employed in a weight ratio to the additional agent within  
25 the range from about 500:1 to about 0.005:1, preferably  
from about 300:1 to about 0.01:1.

Where the antidiabetic agent is a biguanide, the  
compounds of formula I may be employed in a weight ratio to  
biguanide within the range from about 0.01:1 to about  
30 100:1, preferably from about 0.5:1 to about 2:1.

The compounds of formula I may be employed in a  
weight ratio to a glucosidase inhibitor within the range  
from about 0.01:1 to about 100:1, preferably from about  
0.5:1 to about 50:1.

35 The compounds of formula I may be employed in a  
weight ratio to a sulfonylurea in the range from about  
0.01:1 to about 100:1, preferably from about 0.2:1 to about  
10:1.

5           The compounds of formula I may be employed in a weight ratio to a thiazolidinedione in an amount within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1.

          The thiazolidinedione may be employed in amounts  
10 within the range from about 0.01 to about 2000 mg/day, which may optionally be administered in single or divided doses of one to four times per day.

          Further, where the sulfonylurea and thiazolidinedione are to be administered orally in an amount of less than  
15 about 150 mg, these additional agents may be incorporated into a combined single tablet with a therapeutically effective amount of the compounds of formula I.

          Metformin, or salt thereof, may be employed with the compounds of formula I in amounts within the range from  
20 about 500 to about 2000 mg per day, which may be administered in single or divided doses one to four times daily.

          The compounds of formula I may be employed in a weight ratio to a PPAR-alpha agonist, a PPAR-gamma agonist,  
25 a PPAR-alpha/gamma dual agonist, an SGLT2 inhibitor and/or an  $\alpha$ 2 inhibitor within the range from about 0.01:1 to about 100:1, preferably from about 0.5:1 to about 5:1.

          An MTP inhibitor may be administered orally with the compounds of formula I in an amount within the range of  
30 from about 0.01 mg/kg to about 100 mg/kg and preferably from about 0.1 mg/kg to about 75 mg/kg, one to four times daily.

          A preferred oral dosage form, such as tablets or capsules, may contain the MTP inhibitor in an amount of  
35 from about 1 to about 500 mg, preferably from about 2 to about 400 mg, and more preferably from about 5 to about 250 mg, administered on a regimen of one to four times daily.



5           For parenteral administration, the MTP inhibitor may be employed in an amount within the range of from about 0.005 mg/kg to about 10 mg/kg and preferably from about 0.005 mg/kg to about 8 mg/kg, administered on a regimen of one to four times daily.

10           A HMG CoA reductase inhibitor may be administered orally with the compounds of formula I within the range of from about 1 to 2000 mg, and preferably from about 4 to about 200 mg.

15           A preferred oral dosage form, such as tablets or capsules, will contain the HMG CoA reductase inhibitor in an amount from about 0.1 to about 100 mg, preferably from about 5 to about 80 mg, and more preferably from about 10 to about 40 mg.

20           A squalene synthetase inhibitor may be administered with the compounds of formula I within the range of from about 10 mg to about 2000 mg and preferably from about 25 mg to about 200 mg.

25           A preferred oral dosage form, such as tablets or capsules, will contain the squalene synthetase inhibitor in an amount of from about 10 to about 500 mg, preferably from about 25 to about 200 mg.

          The compounds of formula I of the invention can be administered orally or parenterally, such as subcutaneously or intravenously, as well as by nasal application, rectally or sublingually to various mammalian species known to be  
30           subject to such maladies, e.g., humans, in an effective amount within the dosage range of about 0.01 µg/kg to about 1000 µg/kg, preferably about 0.1 µg/kg to 100 µg/kg, more preferably about 0.2 µg/kg to about 50 µg/kg (or from about  
35           0.5 to 2500 mg, preferably from about 1 to 2000 mg) in a regimen of single, two or four divided daily doses.

          The compounds of the formula I can be administered for any of the uses described herein by any suitable means, for

5 example, orally, such as in the form of tablets, capsules,  
granules or powders; sublingually; buccally; parenterally,  
such as by subcutaneous, intravenous, intramuscular, or  
intrasternal injection or infusion techniques (e.g., as  
sterile injectable aqueous or non-aqueous solutions or  
10 suspensions); nasally, including administration to the  
nasal membranes, such as by inhalation spray; topically,  
such as in the form of a cream or ointment; or rectally  
such as in the form of suppositories; in dosage unit  
formulations containing non-toxic, pharmaceutically  
15 acceptable vehicles or diluents. The present compounds  
can, for example, be administered in a form suitable for  
immediate release or extended release. Immediate release  
or extended release can be achieved by the use of suitable  
pharmaceutical compositions comprising the present  
20 compounds, or, particularly in the case of extended  
release, by the use of devices such as subcutaneous  
implants or osmotic pumps. The present compounds can also  
be administered liposomally.

Exemplary compositions for oral administration include  
25 suspensions which can contain, for example,  
microcrystalline cellulose for imparting bulk, alginic acid  
or sodium alginate as a suspending agent, methylcellulose  
as a viscosity enhancer, and sweeteners or flavoring agents  
such as those known in the art; and immediate release  
30 tablets which can contain, for example, microcrystalline  
cellulose, dicalcium phosphate, starch, magnesium stearate  
and/or lactose and/or other excipients, binders, extenders,  
disintegrants, diluents and lubricants such as those known  
in the art. The compounds of formula I can also be  
35 delivered through the oral cavity by sublingual and/or  
buccal administration. Molded tablets, compressed tablets  
or freeze-dried tablets are exemplary forms which may be  
used. Exemplary compositions include those formulating the

5 present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an  
10 excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934).  
15 Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which can  
20 contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration  
25 include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or wetting  
30 and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

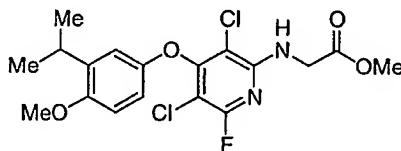
Exemplary compositions for rectal administration include suppositories which can contain, for example, a  
35 suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

5 Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition.

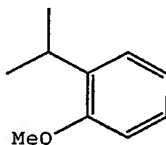
The following working examples serve to better illustrate, but not limit, some of the preferred embodiments of the present invention.

Example 1



25 **3,5-dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylmethylaminopyridine**

Compound 1a: 2-Isopropylanisole

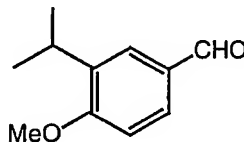


To a solution of 2-isopropylphenol (30g, 220.3 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (300 mL) was added tetrabutylammonium hydrogen

5 sulfate (7.5g, 22.1 mmol). After the entire solid was dissolved, a solution of potassium hydroxide (61.8 g, 1.1 mol in 300 mL H<sub>2</sub>O) was added to the previous mixture. After 15 minutes of stirring, methyl iodide (47g, 20.6 mL, 331 mmol) was added. The mixture was left to stir overnight  
10 (ca. 15 hours). The organic layer was separated and then washed with brine (2 x 100 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The solid material in the concentrate was removed by filtration. The precipitate was washed with hexane (100 mL). The filtrate was concentrated  
15 in vacuo to give 32.15 g of yellow oil as a crude product. The crude product was filtered through a pad of silica gel (250 g) and washed with 5 % EtOAc in hexane to give 30.7 g (93%) of compound 1a as a colorless oil.

20 <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 7.21 (d, 1H, J = 7.7 Hz), 7.16 (t, 1H, J = 7.7 Hz), 6.92 (t, 1H, J = 7.7 Hz), 6.84 (d, 1H, J = 8.3 Hz), 3.82 (s, 3H), 3.27 (septet, 1H, 7 Hz), 1.205 (d, 6H, J = 6.6 Hz)

25 Compound 1b: 3-Isopropyl-4-methoxybenzaldehyde

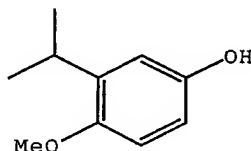


To a 3-necked flask containing 2-isopropylanisole (14g, 93.2 mmol) was added phosphorus oxychloride (57.6 g, 35 mL, 375.5 mmol). The mixture was heated to 80°C and maintained at this temperature while N,N-dimethylformamide (27.4 g, 29 mL, 374.5 mmol) was slowly added using an addition funnel. After the DMF addition, the mixture was heated to 95°C and  
35 maintained at this temperature overnight (ca. 19 h). After cooling to RT, the mixture was poured into a flask

5 containing ice and H<sub>2</sub>O (200 mL) and stirred for ca. 15 min. The product was partitioned with EtOAc (300 mL) and brine (200 mL). The EtOAc extract was separated, washed with brine (2 x 150 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by chromatography  
10 (250 g silica gel, 10% EtOAc in hexane) to afford 13 g (78%) of compound 1b as a yellow oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 9.87 (s, 1H), 7.755 (d, 1H, J = 1.6 Hz), 7.695 (dd, 1H, J = 8.8 Hz, 1.6 Hz), 6.94 (d, 1H, J = 8.3 Hz), 3.91 (s, 3H), 3.31 (septet, 1H, 7 Hz), 1.225 (d, 6H, J = 7.1 Hz)

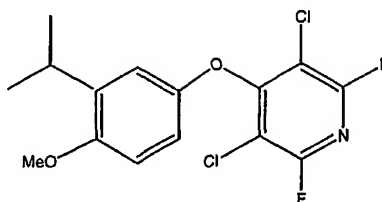
Compound 1c: 3-Isopropyl-4-methoxyphenol



To a solution of 3-isopropyl-4-methoxybenzaldehyde (12.5 g, 70 mmol) in MeOH (140 mL) was added concentrated sulfuric acid (1.2 mL) followed by dropwise addition of 30%  
25 by wt aqueous hydrogen peroxide (6g, 20 mL, 176 mmol). The mixture was left to stir at ambient room temperature. After 3 hours, the mixture was concentrated in vacuo to about 1/3 of the reaction volume. The concentrate was partitioned between EtOAc (100 mL) and brine (50 mL). The EtOAc extract  
30 was washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to give 13.5 g of dark oil as crude product. The crude product was purified by chromatography (250 g silica gel, 10% EtOAc in hexane) to afford 10.1g (86%) of compound 1c as a thick oil that eventually  
35 solidified.

5  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 6.715 (d, 1H,  $J = 2.8$  Hz), 6.705 (d, 1H,  $J = 3.3$  Hz), 6.595 (dd, 1H,  $J = 8.8$  Hz, 3.3 Hz), 4.44 (s, 1H), 3.77 (s, 3H), 3.27 (septet, 1H, 7 Hz), 1.175 (d, 6H,  $J = 7.2$  Hz)

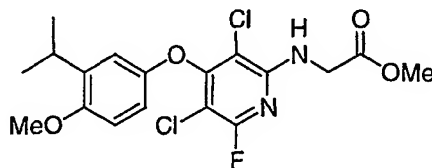
10 Compound 1d: 3,5-Dichloro-2,6-difluoro-4-(3-isopropyl-4-methoxyphenoxy)pyridine



15 To a solution of 3-isopropyl-4-methoxyphenol (0.68 g) and 3,5-dichloro-2,4,6-trifluoropyridine (0.84 g) in DMF (4.0 mL) was added potassium carbonate powder (0.67 g) in one portion. The resulting mixture was stirred at ambient temperature for 1 h. The reaction mixture was diluted with  
20 brine, extracted with ethyl acetate (50 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo to afford compound 1d as an off-white solid (1.15 g, 80%).

25  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 6.87 (d, 1H,  $J = 3.3$  Hz), 6.73 (d, 1H,  $J = 8.8$  Hz), 6.55 (dd, 1H,  $J = 8.8$  Hz, 3.3 Hz), 3.80 (s, 3H), 3.29 (septet, 1H, 7 Hz), 1.18 (d, 6H,  $J = 7.2$  Hz).

30 Compound 1e: 3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylmethylaminopyridine



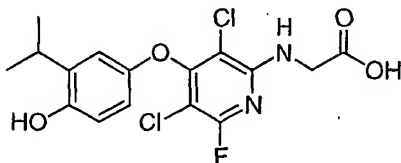
5

To a solution of 3,5-dichloro-2,6-difluoro-4-(3-isopropyl-4-methoxyphenoxy)pyridine. (584 mg) and glycine methyl ester hydrochloric acid (220 mg) in DMF (5.0 mL) was added potassium carbonate powder (500 mg) in one portion. The resulting mixture was stirred at ambient temperature for 20 hours. The reaction mixture was diluted with brine, extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL x 3), dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. Chromatography with ethyl acetate-hexanes (0 - 50% gradient elution) afforded the title compound as a colorless oil (434 mg, 62%).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 6.89 (d, 1H,  $J = 3.3$  Hz), 6.71 (d, 1H,  $J = 8.8$  Hz), 6.54 (dd, 1H,  $J = 8.8$  Hz, 3.3 Hz), 5.70 (br. t, 1H,  $J = 5$  Hz), 4.21 (d, 2H,  $J = 5$  Hz), 3.80 (s, 3H), 3.78 (s, 3H), 3.28 (septet, 1H, 7 Hz), 1.18 (d, 6H,  $J = 7.2$  Hz).

#### Example 2

25



#### 3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethylaminopyridine

30

To a solution of 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonyl-methylaminopyridine (100 mg) in  $\text{CH}_2\text{Cl}_2$  was added a solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  (1 mL, 1.0 M) at ambient temperature. The resulting mixture was stirred for 30 min., poured to



5 stirring water (50 mL), extracted with  $\text{CH}_2\text{Cl}_2$  (20 mL x 3)  
from water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dryness under  
reduced pressure. The residue was dissolved in  $\text{THF}:\text{MeOH}:\text{H}_2\text{O}$   
= 3:1:1 (5 mL), treated with a solution of  $\text{LiOH}$  in water (1  
mL, 1.0 M) and stirred at ambient temperature for 30 min.  
10 The reaction mixture was diluted with a 1.0 M solution of  
 $\text{HCl}$  (50 mL), extracted with ethyl acetate (50 mL x 3), dried  
( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure.  
Purification by HPLC provided the title compound as a white  
solid (80 mg).

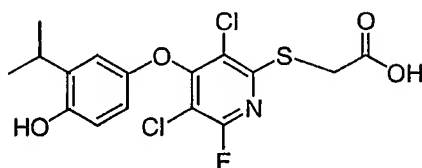
15  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 6.85 (d, 1H,  $J = 3.3$  Hz), 6.64  
(d, 1H,  $J = 8.8$  Hz), 6.47 (dd, 1H,  $J = 8.8$  Hz, 3.3 Hz), 5.63  
(br. t, 1H,  $J = 5$  Hz), 4.29 (d, 2H,  $J = 5$  Hz), 3.17  
(septet, 1H, 7 Hz), 1.23 (d, 6H,  $J = 7.2$  Hz).

20

Examples 3-13 were prepared by a similar procedure as  
described in Example 1, but with the following variations:

Example 3

25



**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-  
hydroxycarbonylmethylthiopyridine**

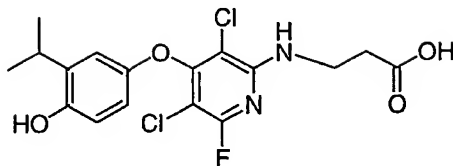
30

By use of methyl mercaptoacetate in place of glycine  
methyl ester for the preparation of Compound 1e followed by  
deprotection as described for example 2.

$(\text{M-H})^- = 403.87$

35 molecular weight (MW) = 406.26

5

Example 4

10     **3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(2-hydroxycarbonylethylamino)pyridine**

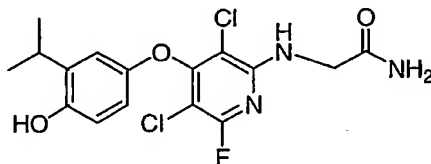
By use of  $\beta$ -alanine methyl ester in place of glycine methyl ester for the preparation of Compound 1e followed by  
15 deprotection as described for example 2.

(M-H)<sup>-</sup> = 400.9

MW = 403.24

Example 5

20



**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(2-aminocarbonylmethylamino)pyridine**

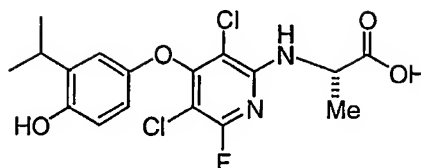
25

By use of glycinamide in place of glycine methyl ester for the preparation of Compound 1e followed by deprotection as described for example 2.

(M-H)<sup>-</sup> = 386

30     MW = 388.23

5

Example 6

10 **3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(1-methyl-1-hydroxycarbonylmethylaminopyridine**

By use of 1-alanine methyl ester in place of glycine methyl ester ester for the preparation of Compound 1e followed by deprotection as described for example 2.

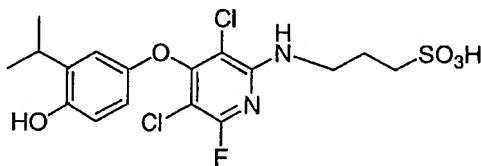
15 Satisfactory  $^1\text{H-NMR}$  and MS data were obtained.

$(\text{M-H})^- = 401$

MW = 403.24

Example 7

20



25 **3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(3-hydroxysulfonylpropylamino)pyridine**

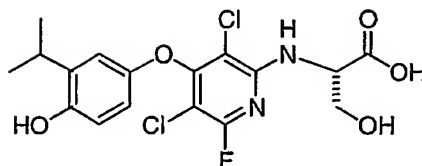
30

By use of 3-aminopropylsulfonic acid in place of glycine methyl ester ester for the preparation of Compound 1e followed by deprotection as described for example 2.

$(\text{M-H})^- = 451$

MW = 453.32

5

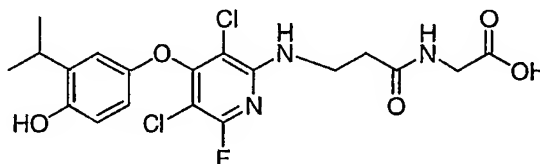
Example 8

10 **3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(1-hydroxycarbonyl-2-hydroxyethylamino)pyridine**

By use of l-serine methyl ester in place of glycine methyl ester for the preparation of Compound 1e followed by deprotection as described for example 2.

15  $(M+H)^+ = 417$

MW = 419.24

Example 9

20

**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(3-hydroxycarbonylmethylamino-3-oxopropylamino)pyridine**

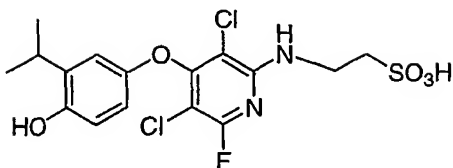
25 By use of  $\beta$ -alanyl-glycine in place of glycine methyl ester for the preparation of Compound 1e followed by deprotection as described for example 2.

$(M-H)^- = 458$

MW = 460.29

30

5

Example 10

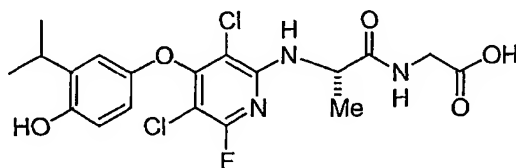
10

**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(2-hydroxysulfonyl-ethylamino)pyridine**

By use of 2-aminoethylsulfonic acid in place of glycine methyl ester for the preparation of Compound 1e followed by deprotection as described for example 2.

15  $(M-H)^- = 439.29$ 

MW = 437

Example 11

20

**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(2-hydroxycarbonylmethylamino-2-oxo-1-methylethylamino)pyridine**

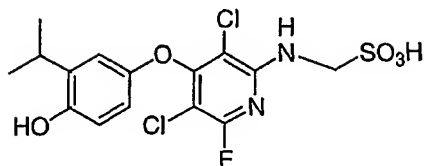
25

By use of 1-alanyl-glycine methyl ester in place of glycine methyl ester for the preparation of Compound 1e followed by deprotection as described for example 2.

 $(M-H)^- = 458$ 

30 MW = 560.29

5

Example 12

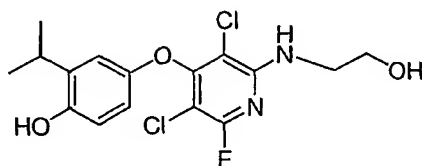
10

**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-hydroxysulfonylmethylaminopyridine**

By use of aminomethanesulfonic acid in place of glycine methyl ester for the preparation of Compound 1e followed by deprotection as described for example 2.

15 (M-H)<sup>-</sup> = 423

MW = 425.27

Example 13

20

**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-(2-hydroxyethylamino)pyridine**

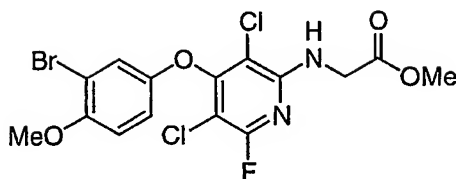
25 By reduction of the methyl ester of 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethylaminopyridine (example 2), with Dibal-H in THF.

(M-H)<sup>-</sup> = 423

MW = 425.27

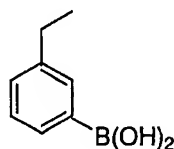
30

5

Example 14

**3,5-dichloro-2-fluoro-4-[3-bromo-4-methoxy-phenoxy]-6-methoxycarbonylmethyl-aminopyridine**

10 Compound 14a: 3-Ethylphenylboronic acid

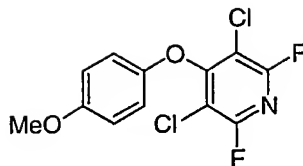


To a solution of 3-bromo-1-ethylbenzene (1.0 g) in THF  
15 (10 mL) at -78°C under argon was added a solution of n-BuLi  
(2.5 M, 2.5 mL) in hexanes in dropwise fashion. The mixture  
was stirred at -78°C for 10 min. and treated with 1.35 mL of  
tri-isopropylborate (neat) dropwise. The reaction mixture  
was allowed to warm up to 10°C over a period of 3 hours  
20 while stirring. The mixture was then quenched carefully  
with 1 N HCl (100 mL) solution and extracted with ethyl  
acetate (100 mL x 2). The combined organic layers were  
dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure.  
Chromatography with ethyl acetate-hexanes (0-100% gradient  
25 elution) provided compound 14a as a white solid (0.4 g).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 8.06 (m, 2H), 7.44 (m, 2H), 2.77  
(q, 2H, J = 7.0 Hz), 1.32 (t, 3H, J = 7.0 Hz).

30 Compound 14b: 3,5-Dichloro-2,6-difluoro-4-(4-methoxy-  
phenoxy)pyridine

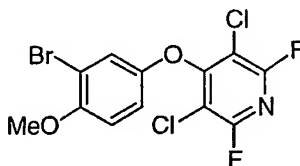
5



To a solution of 4-methoxyphenol (1.25 g) and 3,5-dichloro-2,4,6-trifluoropyridine (2.05 g) in DMF (10.0 mL) was added potassium carbonate powder (1.50 g) in one portion. The resulting mixture was stirred at ambient temperature for 3 hours. The reaction mixture was diluted with brine and extracted with ethyl acetate (100 mL x 3). The combined organic layers were washed with brine (100 mL x 3), dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo to provide compound 14b as a white solid (3.0 g).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 6.78 (m, 4H), 3.72 (s, 3H).

20 Compound 14c: 3,5-Dichloro-2,6-difluoro-4-(3-bromo-4-methoxy-phenoxy)pyridine



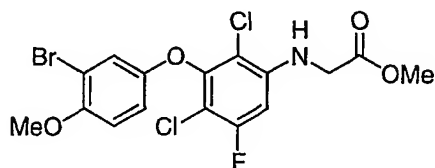
25 To a solution of 3,5-dichloro-2,6-difluoro-4-(4-methoxyphenoxy)pyridine (0.94 g) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added neat bromine (1.0 g). The mixture was stirred at ambient temperature for 1 h. The solvent and excess bromine were removed under reduced pressure. Chromatography with ethyl acetate-hexanes (0-50% gradient elution) provides compound 14c (0.25 g).



5  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.14 (d, 1H,  $J = 2.7$  Hz), 6.82 (m, 2H), 3.87 (s, 3H).

Compound 14d: 3,5-Dichloro-2-fluoro-4-(3-bromo-4-methoxyphenoxy)-6-methoxycarbonylmethylaminopyridine

10

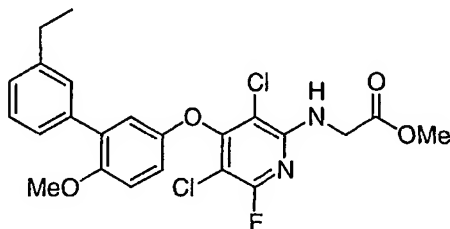


To a solution of 3,5-dichloro-2,6-difluoro-4-(3-bromo-4-methoxyphenoxy)pyridine (250 mg) and glycine methyl ester hydrochloric acid (150 mg) in DMF (2.0 mL) was added potassium carbonate powder (250 mg) in one portion. The resulting mixture was stirred at ambient temperature for 20 hours. The reaction mixture was diluted with brine and extracted with ethyl acetate (50 mL x 2). The combined organic layers were washed with brine (50 mL x 3), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Chromatography with ethyl acetate-hexanes (0 - 50% gradient elution) provided the title compound as a white solid (253 mg).

25  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.13 (d, 1H,  $J = 2.7$  Hz), 6.82 (m, 2H), 5.70 (br. t, 1H,  $J = 5.0$  Hz), 4.24 (d, 2 H,  $J = 5$  Hz), 3.87 (s, 3H), 3.81 (s, 3H).

#### Example 15

30



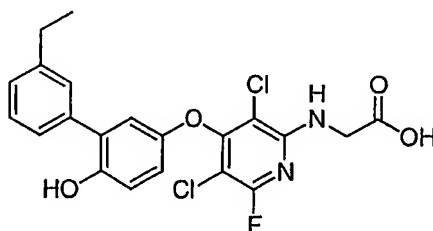
5

**3,5-Dichloro-2-fluoro-4-[3-(3-ethylphenyl)-4-methoxy-  
phenoxy]-6-methoxycarbonylmethylaminopyridine**

To a solution of 3,5-dichloro-2,6-difluoro-4-(3-bromo-  
10 4-methoxyphenoxy)-6-methoxycarbonyl-methylaminopyridine (253  
mg) and 3-ethylphenylboronic acid (100 mg) in THF (10.0 mL)  
was added a solution of sodium carbonate (2.0 M in water,  
1.0 mL). The resulting mixture was degassed with argon,  
treated with tetrakis(triphenylphosphine) palladium (30 mg)  
15 and stirred at reflux in dark for 18 hours. Cooled reaction  
mixture was diluted with brine, neutralized with 1 N HCl and  
extracted with ethyl acetate (50 mLx 3). The combined  
organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated.  
Chromatography with ethyl acetate-hexanes (0 - 50% gradient  
20 elution) afforded the title compound as a light yellow oil  
(180 mg).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 7.32 (m, 3H), 7.19 (m, 1H), 6.90  
(m, 2H), 6.82 (m, 1H), 5.69 (br. t, 1 H, J = 5 Hz), 4.21 (d,  
25 2 H, J = 5 Hz), 3.80 (s, 3H), 3.78 (s, 3H), 2.69 (q, 2H, 7  
Hz), 1.27 (t, 3H, J = 7 Hz).

Example 16



30

**3,5-Dichloro-2-fluoro-4-[3-(3-ethylphenyl)-4-hydroxy-  
phenoxy]-6-hydroxycarbonylmethylaminopyridine**

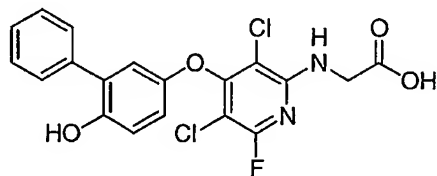
5 To a solution of 3,5-dichloro-2-fluoro-4-[3-(3-ethylphenyl)-4-methoxyphenoxy]-6-methoxycarbonylmethylaminopyridine (50 mg) in  $\text{CH}_2\text{Cl}_2$  was added a solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  (0.5 mL, 1.0 M) at ambient temperature. The resulting mixture was stirred for 30 min. The reaction  
10 mixture was diluted with a 1.0 M solution of HCl (50 mL), extracted with ethyl acetate (50 mL x 3), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Purification by HPLC afforded the title compound as a yellow oil (32 mg).

15  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.41 (m, 1H), 7.26 (m, 3H), 6.92 (m, 1H), 6.80 (m, 2H), 5.63 (br. t, 1 H,  $J = 5$  Hz), 5.18 (br. s, 2H), 4.29 (d, 2 H,  $J = 5$  Hz), 2.70 (q, 2H, 7 Hz), 1.27 (t, 3H,  $J = 7$  Hz).

20 Examples 17-21 were prepared by a similar procedure as described in Examples 14 through 16, but with the following variations.

Example 17

25



**3,5-Dichloro-2-fluoro-4-(3-phenyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethylaminopyridine**

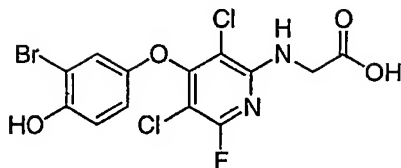
30

By use of phenylboronic acid in place of 3-ethylphenylboronic acid in example 15 followed by deprotection as described for example 16.

$(\text{M}-\text{H})^- = 421$

35 MW = 423.23

5

Example 18

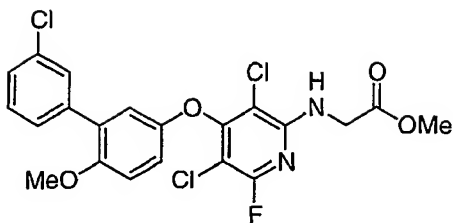
10      **3,5-Dichloro-2-fluoro-4-[3-(3-bromo-4-hydroxyphenoxy)-6-**  
         **hydroxycarbonylmethyl-aminopyridine**

         By direct deprotection of 3,5-dichloro-2-fluoro-4-(3-  
bromo-4-methoxy-phenoxy)-6-methoxycarbonylmethylamino-  
15 pyridine using the procedure as described for example 16.

(M-H)<sup>-</sup> = 424.8

MW = 426.03

5

Example 19

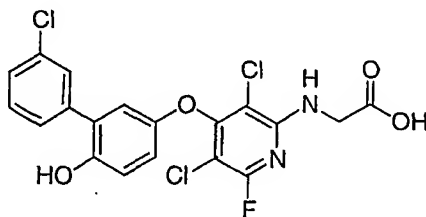
10

**3,5-Dichloro-2-fluoro-4-[3-(3-chlorophenyl)-4-methoxyphenoxy]-6-(2-methoxycarbonylethylamino)pyridine**

By use of 3-chlorophenylboronic acid in place of 3-ethylphenylboronic acid in the procedure as described for example 15.

15  $(M-H)^- = 484.7$ 

MW = 485.73

Example 20

20

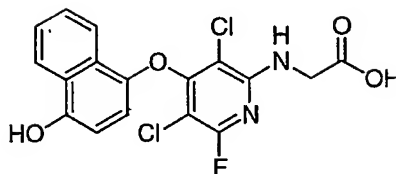
**3,5-dichloro-2-fluoro-4-[3-(3-chlorophenyl)-4-hydroxyphenoxy]-6-(hydroxycarbonylmethylamino)pyridine**

25 By direct deprotection of example 19 using the procedure as described for example 16.

 $(M-H)^- = 455$ 

MW = 457.7

5

Example 21

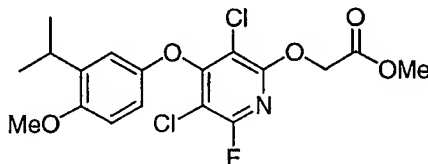
10

**3,5-Dichloro-2-fluoro-4-(4-hydroxynaphthoxy)-6-hydroxycarbonylmethylamino-pyridine**

By use of 4-methoxynaphthol in place of 4-methoxyphenol using the procedure as described to prepare compound 14b followed by deprotection as described for example 2.

15 (M-H)<sup>-</sup> = 395

MW = 397.19

Example 22

20

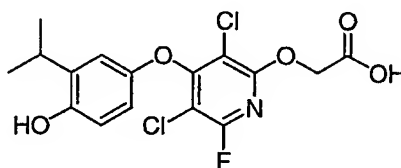
**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylmethoxypyridine**

25 To a solution of 3,5-dichloro-2,6-difluoro-4-(3-isopropyl-4-methoxyphenoxy)pyridine (100 mg) and methyl glycolate (neat, 25  $\mu$ L) in THF (2.0 mL) was added a 60% oil dispersion of sodium hydride (10 mg) in one portion. The resulting mixture was stirred at ambient temperature for 30 min. The reaction mixture was diluted with brine, 30 neutralized with 1 N HCl, extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mLx 2),

5 dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated in vacuo to afford the title compound as a colorless oil (120 mg).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 6.87 (d, 1H,  $J = 2.7$  Hz), 6.71 (d, 1H,  $J = 8.8$  Hz), 6.52 (dd, 1H,  $J = 8.8$  Hz, 2.7 Hz), 4.94 (s, 2 H), 3.78 (s, 3H), 3.76 (s, 3H), 3.28 (septet, 1H, 7 Hz), 1.18 (d, 6H,  $J = 7$  Hz).

Example 23



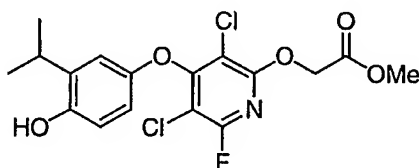
**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethoxypyridine**

20 To a solution of 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylmethoxy-pyridine (120 mg) in  $\text{CH}_2\text{Cl}_2$  (3.0 mL) was added a solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  (1 mL, 1.0 M) at ambient temperature. The resulting mixture was stirred for 2 h, poured to stirring water (50 mL),  
25 extracted with  $\text{CH}_2\text{Cl}_2$  (20 mL x 3) from water, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dryness under reduced pressure. The residue was dissolved in  $\text{THF}:\text{MeOH}:\text{H}_2\text{O} = 3:1:1$  (5 mL), treated with a solution of  $\text{LiOH}$  in water (1 mL, 1.0 M) and stirred at ambient temperature for 30 min. The reaction  
30 mixture was diluted with a 1.0 M solution of  $\text{HCl}$  (50 mL), extracted with ethyl acetate (50 mL x 3), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Purification by HPLC afforded the title compound as a colorless oil (80 mg).

5  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 6.86 (d, 1H,  $J = 2.7$  Hz), 6.66 (d, 1H,  $J = 8.8$  Hz), 6.47 (dd, 1H,  $J = 8.8$  Hz, 2.7 Hz), 6.13 (br. s, 2 H), 5.01 (s, 2 H), 3.17 (septet, 1H, 7 Hz), 1.23 (d, 6H,  $J = 7.2$  Hz).

10 Examples 24-27 were prepared by a similar procedure as described in Example 22, but with the following variations.

Example 24



**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-methoxycarbonylmethoxypyridine**

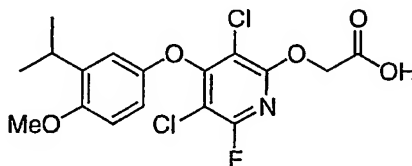
20 Obtained via purification of the intermediate before treatment with LiOH in the procedure for preparation of example 23.

(M-H) $^-$  = 401.8

MW = 409.23

25

Example 25



**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-hydroxycarbonylmethoxypyridine**



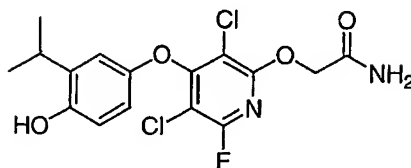
5       The title compound was obtained by LiOH hydrolysis of example 22.

(M-H)<sup>-</sup> = 401.8

MW = 404.23

10

Example 26



15

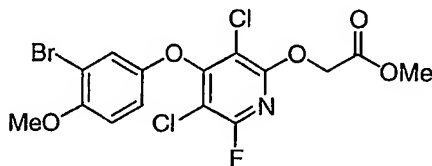
**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenoxy)-6-aminocarbonylmethoxypyridine**

Prepared by use of glycolamide in place of methyl glycolate in the procedure for example 22, followed by BBr<sub>3</sub> deprotection, as described for example 23.

20 (M-H)<sup>-</sup> = 386.9

MW = 389.21

Example 27



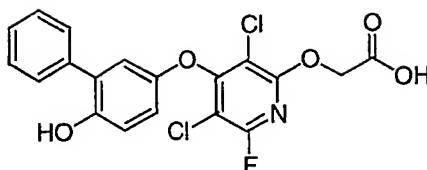
25

**3,5-Dichloro-2-fluoro-4-(3-bromo-4-methoxyphenoxy)-6-methoxycarbonylmethoxypyridine**

30       Prepared by use of 4-(3-bromo-4-methoxyphenoxy)-3,5-dichloro-2,6-difluoropyridine in place of 3,5-dichloro-2,6-difluoro-4-(3-isopropyl-4-methoxyphenoxy)pyridine in the procedure described for example 22.

5 (M+H)<sup>+</sup> = 455.7  
MW = 455.07

Example 28



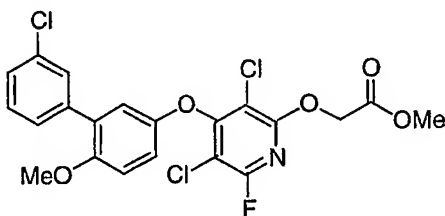
10

**3,5-Dichloro-2-fluoro-4-(3-phenyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethoxypyridine**

15 Prepared by use of 3,5-dichloro-2,6-difluoro-4-(3-bromo-4-methoxyphenoxy)-6-methoxycarbonylmethoxypyridine in place of 3,5-dichloro-2,6-difluoro-4-(3-bromo-4-methoxyphenoxy)-6-methoxycarbonyl-methylaminopyridine in the procedure described for example 17.

20 (M-H)<sup>-</sup> = 421.9  
MW =

Example 29



25

**3,5-Dichloro-2-fluoro-4-[3-(3-chlorophenyl)-4-methoxyphenoxy]-6-methoxycarbonylmethoxypyridine**

30 Prepared by use of 3,5-dichloro-2,6-difluoro-4-(3-bromo-4-methoxyphenoxy)-6-methoxycarbonylmethoxypyridine in

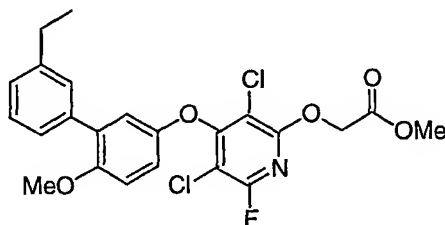
5 place of 3,5-dichloro-2,6-difluoro-4-(3-bromo-4-methoxyphenoxy)-6-methoxycarbonyl-methylaminopyridine in the procedure described for example 19.

(M-H)<sup>-</sup> = 484.8

MW = 486.71

10

Example 30



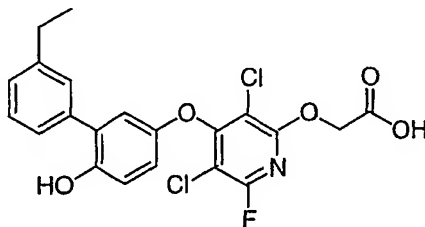
15 **3,5-Dichloro-2-fluoro-4-[3-(3-ethylphenyl)-4-methoxyphenoxy]-6-methoxycarbonylmethoxypyridine**

Prepared by use of 3,5-dichloro-2,6-difluoro-4-(3-bromo-4-methoxyphenoxy)-6-methoxycarbonylmethoxypyridine in place of 3,5-dichloro-2,6-difluoro-4-(3-bromo-4-methoxyphenoxy)-6-methoxycarbonyl-methylaminopyridine in the procedure described for example 15.

MW = 480.32

25

Example 31



30

**3,5-Dichloro-2-fluoro-4-[3-(3-ethylphenyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethoxypyridine**

5

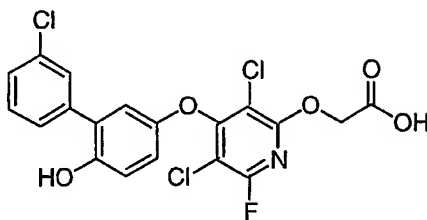
Prepared by deprotection of example 30 using the procedure described for example 16.

$(M-H)^- = 449.8$

MW = 452.27

10

Example 32



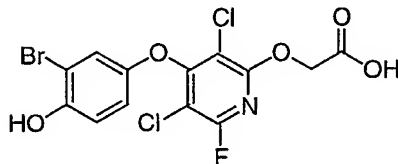
15      **3,5-Dichloro-2-fluoro-4-[3-(3-chlorophenyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethoxypyridine**

Prepared by deprotection of example 29 using the procedure described for example 20.

20       $(M-H)^- = 457.5$

MW = 458.66

Example 33



25

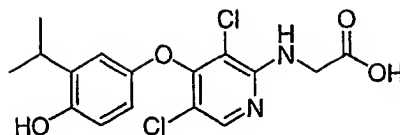
**3,5-Dichloro-2-fluoro-4-[3-bromo-4-hydroxyphenoxy]-6-hydroxycarbonylmethoxypyridine**

30      Prepared by deprotection of example 27 using the procedure described for example 16.

$(M-H)^- = 425.72$

5 MW = 427.01

Example 34

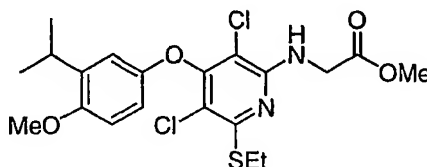


10

**3,5-dichloro-4-(3-isopropyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethylaminopyridine**

Compound 34a: 3,5-Dichloro-2-ethylthio-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylmethylaminopyridine

15



To a solution of 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylmethylaminopyridine (200 mg) in DMF was added ethylthiol (0.1 mL, neat) and potassium carbonate powder (100 mg) at ambient temperature. The resulting mixture was stirred for 4 h at ambient temperature and 4 h at 70°C. Cooled reaction mixture was diluted with brine (100 mL) and extracted with ethyl acetate (50 mL x 3). Combined organic layers were washed with brine (50 mL x 3), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Chromatography with ethyl acetate-hexanes (0-25% gradient elution) afforded compound 34a (130 mg).

20

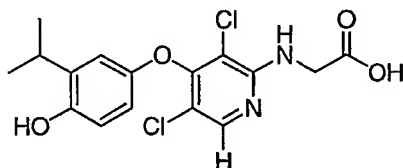
25

30

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 6.90 (d, 1H, J = 2.7 Hz), 6.69 (d, 1H, J = 8.8 Hz), 6.49 (dd, 1H, J = 8.8 Hz, 2.7 Hz), 5.53

5 (br. t, 1 H, J = 5 Hz), 4.24 (d, 2 H, J = 5 Hz), 3.79 (s, 3H), 3.78 (s, 3H), 3.28 (septet, 1H, 7 Hz), 3.11 (q, 2H, J=7 Hz), 1.38 (t, 3H, J=7 Hz), 1.19 (d, 6H, J=7 Hz).

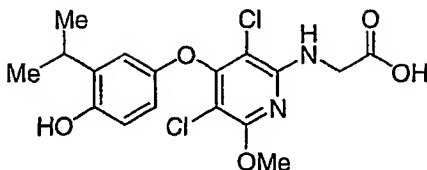
10 Compound 34b: 3,5-Dichloro-4-(3-isopropyl-4-hydroxy-phenoxy)-6-hydroxycarbonylmethylaminopyridine



15 To a suspension of Raney-Nickel (ca. 0.3 g) in ethanol (2 mL) was added a solution of 3,5-dichloro-2-ethylthio-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonyl-methylaminopyridine (122 mg) in ethanol (3 mL) at ambient temperature. The resulting mixture was stirred at reflux for 3 hours. Cooled reaction mixture was filtered  
20 through celite. Filtrate was extracted with ethyl acetate (50 mL x 3) from brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to dryness under reduced pressure. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL), treated with a solution of BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (1 mL, 1.0 M), stirred at ambient temperature for 30 min. The  
25 reaction mixture was diluted with brine (50 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL x 3), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by HPLC afforded the title compound (24 mg).

30 <sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD, δ) 8.02 (s, 1H), 6.71 (d, 1H, J = 2.7 Hz), 6.64 (d, 1H, J = 8.8 Hz), 6.41 (dd, 1H, J = 8.8 Hz, 2.7 Hz), 4.15 (s, 2 H), 3.23 (septet, 1H, 7 Hz), 1.17 (d, 6H, J = 7 Hz).

5

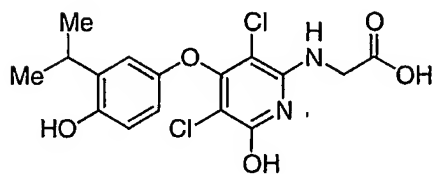
Example 35

10                   **3,5-Dichloro-2-methoxy-4-(3-isopropyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethylaminopyridine**

To a solution of 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylmethylaminopyridine (161 mg) in methanol (3.0 mL) was added a solution of sodium methoxide in methanol (0.5 M, 1.0 mL). The resulting mixture was stirred at ambient temperature for 18 hours, followed by stirring at 80°C for 5 hours. Cooled reaction mixture was then diluted with 1 N HCl (50 mL) and extracted with ethyl acetate (50 mL x 2). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The dried crude product was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3.0 mL) and treated with a solution of BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> (1 mL, 1.0 M) at ambient temperature. The resulting mixture was stirred for 1 hour, poured to stirring water (50 mL), extracted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL x 3) from water, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to dryness under reduced pressure. The residue was dissolved in THF:MeOH:H<sub>2</sub>O = 3:1:1 (3 mL), treated with LiOH in one portion (50 mg) and stirred at ambient temperature for 1 hour. The reaction mixture was diluted with a 1.0 M solution of HCl (50 mL), extracted with ethyl acetate (50 mL x 3), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated under reduced pressure. Purification by HPLC afforded the title compound as a white solid (30 mg).

5  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ) 6.70 (d, 1H,  $J = 3.3$  Hz), 6.62 (d, 1H,  $J = 8.8$  Hz), 6.40 (dd, 1H,  $J = 8.8$  Hz, 3.3 Hz), 4.11 (s, 2H), 3.91 (s, 3H), 3.22 (septet, 1H, 7.2 Hz), 1.16 (d, 6H,  $J = 7.2$  Hz).

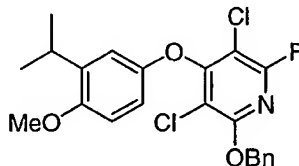
10

Example 36

15

**3,5-Dichloro-2-hydroxy-4-(3-isopropyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethylaminopyridine**

Compound 36a: 2-Benzyloxy-3,5-dichloro-6-fluoro-4-(3-isopropyl-4-methoxyphenoxy)pyridine:



20

To a solution of 3,5-dichloro-2,6-difluoro-4-(3-isopropyl-4-methoxyphenoxy)pyridine (267 mg) and benzyl alcohol (neat, 100  $\mu\text{L}$ ) in THF (2.0 mL) was added a 60% oil dispersion of sodium hydride (50 mg) in one portion. The resulting mixture was stirred at ambient temperature for 30 min. The reaction mixture was diluted with brine, neutralized with 1 N HCl (50 mL), extracted with  $\text{CH}_2\text{Cl}_2$  (50 mLx 2), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated.

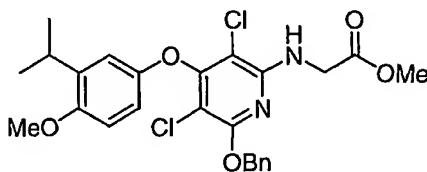
30 Chromatography with ethyl acetate-hexanes (0-25% gradient elution) afforded compound 36a as a colorless oil (240 mg).



5  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.49 (d, 2H,  $J = 7.0$  Hz), 7.39 (t, 2H,  $J = 7.0$  Hz), 7.35 (t, 1H,  $J = 7.0$  Hz), 6.88 (d, 1H,  $J = 2.7$  Hz), 6.72 (d, 1H,  $J = 8.8$  Hz), 6.53 (dd, 1H,  $J = 8.8$  Hz, 2.7 Hz), 5.44 (s, 2H), 3.79 (s, 3H), 3.29 (septet, 1H, 7 Hz), 1.18 (d, 6H,  $J = 7$  Hz).

10

Compound 36b: 2-Benzyloxy-3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylaminopyridine



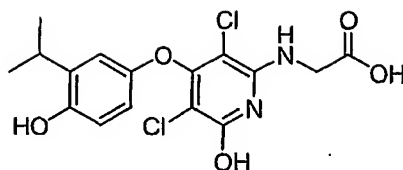
15

To a solution of 2 benzyloxy-3,5-dichloro-6-fluoro-4-(3-isopropyl-4-methoxyphenoxy)pyridine (98 mg) in DMSO was added glycine methyl ester hydrochloric acid salt (108 mg) and potassium carbonate (200 mg). The mixture was stirred at 100°C for 2 hours. Cooled reaction mixture was diluted with 1 N HCl (50 mL), extracted with ethyl acetate (50 mL x 2). Combined extracts were washed with 1 N HCl (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Chromatography with ethyl acetate-hexanes (0-100% gradient elution) afforded compound 36b as a colorless oil (60 mg).

20  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.44 (d, 2H,  $J = 7.0$  Hz), 7.37 (t, 2H,  $J = 7.0$  Hz), 7.32 (t, 1H,  $J = 7.0$  Hz), 6.90 (d, 1H,  $J = 2.7$  Hz), 6.70 (d, 1H,  $J = 8.8$  Hz), 6.53 (dd, 1H,  $J = 8.8$  Hz, 2.7 Hz), 5.46 (t, 1H,  $J = 5.0$  Hz.), 5.40 (s, 2H), 4.19 (d, 2H,  $J = 5.0$  Hz), 3.78 (s, 3H), 3.77 (s, 3H), 3.29 (septet, 1H, 7 Hz), 1.19 (d, 6H,  $J = 7$  Hz).

35 Compound 36c: 3,5-Dichloro-2-hydroxy-6-hydroxycarbonyl-amino-4-(3-isopropyl-4-hydroxyphenoxy)pyridine

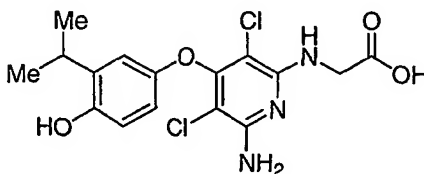
5



To a solution of 2 benzyloxy-3,5-dichloro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylamino-pyridine (60 mg) in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) was added a solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  (2 mL, 1.0 M) at ambient temperature. The resulting mixture was stirred for 1.5 hours, poured to stirring water (50 mL), extracted with  $\text{CH}_2\text{Cl}_2$  (20 mL x 3) from 1 N HCl (50 mL, major solubility problem), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dryness under reduced pressure. The residue was dissolved in THF (3 mL), treated with a solution of LiOH in water (1 mL, 1.0 M) and stirred at ambient temperature for 3 hours. The reaction mixture was diluted with a 1.0 M solution of HCl (50 mL), extracted with ethyl acetate (50 mL x 3), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure. Purification by HPLC afforded the title compound as a white solid (5 mg).

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ) 6.71 (d, 1H,  $J = 2.7$  Hz), 6.62 (d, 1H,  $J = 8.8$  Hz), 6.41 (dd, 1H,  $J = 8.8$  Hz, 2.7 Hz), 4.13 (s, 2 H), 3.23 (septet, 1H, 7 Hz), 1.16 (d, 6H,  $J = 7.2$  Hz).

#### Example 37

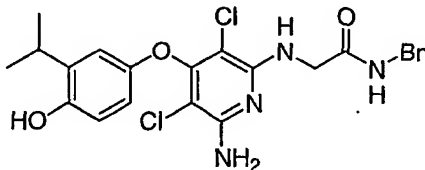


30

5        **2-Amino-3,5-dichloro-6-hydroxycarbonylmethylamino-4-(3-isopropyl-4-hydroxyphenoxy)pyridine**

Compound 37a: 2-Amino-6-benzylaminocarbonylmethylamino-3,5-dichloro-4-(3-isopropyl-4-hydroxyphenoxy)pyridine.

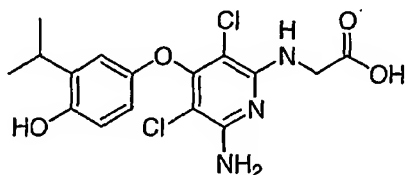
10



To a solution of 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenoxy)-6-methoxycarbonylmethylamino-  
15 pyridine (80 mg) and benzyl amine (neat, 100  $\mu$ L) in methanol (2.0 mL) was added potassium carbonate (200 mg) in one portion. The resulting mixture was stirred at 80°C for 20 hours. Cooled reaction mixture was diluted with brine, extracted with ethyl acetate (50 mL x 2), dried ( $\text{Na}_2\text{SO}_4$ ), and  
20 concentrated. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (5.0 mL) and treated with a solution of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  (2 mL, 1.0 M) at ambient temperature. The resulting mixture was stirred for 2 hours, poured to stirring 1 N HCl (50 mL), extracted with ethyl acetate (20 mL x 3) from 1 N HCl (50 mL, major  
25 solubility problem, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to dryness under reduced pressure. Purification by HPLC afforded compound 37a (35 mg).

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ) 7.25 (m, 5H), 6.70 (d, 1H,  $J = 2.7$  Hz), 6.59 (d, 1H,  $J = 8.8$  Hz), 6.38 (dd, 1H,  $J = 8.8$  Hz, 2.7 Hz), 4.41 (s, 2 H), 4.03 (s, 2H), 3.20 (septet, 1H, 7Hz), 1.14 (d, 6H,  $J = 7.2$  Hz).

- 5 Compound 37b: 2-Amino-3,5-dichloro-4-(3-isopropyl-4-hydroxy-phenoxy)-6-hydroxycarbonylaminopyridine



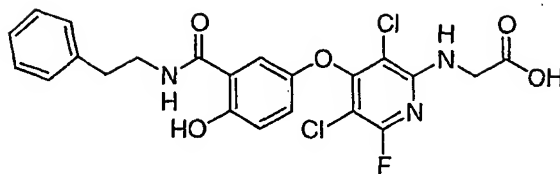
- 10 To a solution of 2-amino-6-benzylaminocarbonyl-methylamino-3,5-dichloro-4-(3-isopropyl-4-hydroxy-phenoxy)pyridine (35 mg) in methanol (5 mL) was added concentrated sulfuric acid (0.3 mL). The resulting mixture was stirred at reflux for 18 hours. Cooled reaction mixture  
15 was diluted with water (50 mL) and extracted with ethyl acetate (50 mL x 2). Combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated under reduced pressure to afford the methyl ester as a light yellow oil (25 mg). This intermediate was dissolved in methanol (3.0 mL), treated with a solution of  
20 LiOH in water (1.0M, 1.0 mL), stirred at ambient temperature for 1h, diluted with 1N HCl (50 mL), extracted with EtOAc (50 mL x 2), dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. Preparative HPLC purification afforded the title compound as a white solid (23 mg).

25

$^1\text{H}$  NMR (500 MHz  $\text{CD}_3\text{OD}$ ,  $\delta$ ) 6.71 (d, 1H,  $J = 2.7$  Hz), 6.62 (d, 1H,  $J = 8.8$  Hz), 6.41 (dd, 1H,  $J = 8.8$  Hz, 2.7 Hz), 4.13 (s, 2 H), 3.23 (septet, 1H, 7 Hz), 1.15 (d, 6H,  $J = 7.2$  Hz).

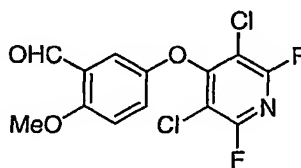
30

5

Example 38

10 **3,5-Dichloro-2-fluoro-4-[3-(phenethylaminocarbonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethylaminopyridine**

Compound 38a: 3,5-dichloro-2,6-difluoro-4-[3-formyl-4-methoxyphenoxy]pyridine



15

3,5-dichloro-2,6-difluoro-4-(4-methoxyphenoxy)-pyridine (0.31g, 1 mmol) was dissolved in 7 mL of methylenechloride and cooled to -58°C under argon.

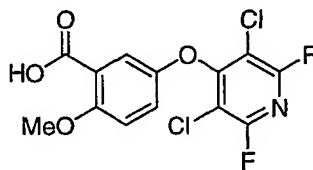
20 Dichloromethyl methyl ether (0.18 mL, 2mmol) was added, followed by dropwise addition of an 1.0 M tin chloride solution in methylenechloride (6 mL). The reaction mixture was stirred for 5 hrs at 0°C then quenched by the addition of 3 mL of 1N HCl. After stirring for 30 minutes, product

25 was extracted 2X with 50 mL portions of methylene chloride. The product was purified by silica gel chromatography using 10% ethyl acetate in hexanes. The appropriate fractions were combined and concentrated to yield 0.26g (77%) of compound 38a. M.P. 111-112°C.

30

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 7.25-7.20 (2H, m), 7.02 (1H, d, J 8.78 Hz), 3.94 (3H, s), 10.41(1H, s)

- 5 Compound 38b: 3,5-Dichloro-2,6-difluoro-4-[3-(hydroxy-carbonyl)-4-methoxyphenoxy]pyridine

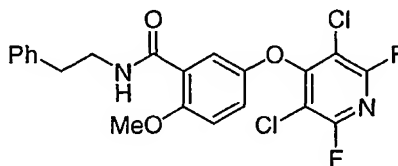


- 10 Sulfamic acid (0.74 mL, of 1M solution) was added to a 1 mL THF solution of compound 38a (0.1308g, 0.392 mmol). This was cooled to 5°C and sodium chlorite (71 mg, 57.6 mg) in 0.4 mL of water was added dropwise. After addition, the reaction was stirred at room temperature for 1 hr, diluted  
15 with 100 mL of CH<sub>2</sub>Cl<sub>2</sub> and 4 mL of water. The organic layer was separated, washed with water, brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo to yield 0.133 g of compound 38b as a white solid. M.P. 141-149°C.

- 20 <sup>1</sup>H NMR (CDCl<sub>3</sub>) 7.57 (1H, d J 3.30Hz), 7.25 (1H, dd J 9.35, 3.30 Hz), 7.09 (1H, J 8.80 Hz), 4.09 (3H, s)

Compound 38c: 3,5-Dichloro-2,6-difluoro-4-[3-(phenethyl-aminocarbonyl)-4-methoxyphenoxy]pyridine

25

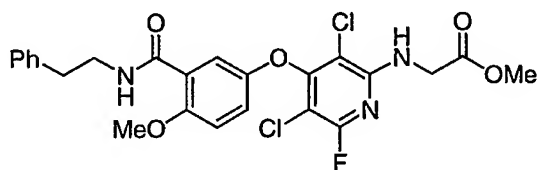


- Compound 38b (50 mg, 0.143 mmol), phenethylamine (23.2 mg, 0.185 mmol), hydroxybenzotriazole (21.6 mg, 0.16  
30 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbo-diimide HCl were stirred in 2mL of methylene chloride and 0.2 mL of DMF for 1 hr. The reaction mixture was diluted with 20 mL of methylenechloride and the organic solution was washed

5 with water (2x), brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated to yield 62.5 mg (96%) of compound 38c as a foam.

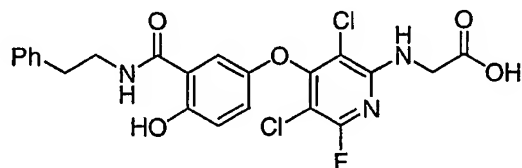
$^1\text{H}$  NMR( $\text{CDCl}_3$ )  $\delta$  7.90 (1H, br s), 7.58 (1H, d, J 4.30 Hz),  
10 7.28-7.25 (2H, m), 7.19-7.17 (3H, m), 7.01 (1H, dd, J 3.30, 9.35 Hz), 6.85 (1H, d 8.80 Hz), 3.68-3.65 (5H, m), 2.83 (2H, t, 7.15 Hz).

Compound 38d: 3,5-Dichloro-2-fluoro-4-[3-(phenethylamino-  
15 carbonyl)-4-methoxyphenoxy]-6-methoxycarbonylmethylamino pyridine



20 3,5-Dichloro-2,6-difluoro-4-[3-(phenethylamino-carbonyl)-4-methoxyphenoxy]pyridine (64.7 mg), glycine methyl ester HCl (35.2 mg) and potassium carbonate (58 mg) were stirred at room temperature for 2 hrs then at 50°C for 30 minutes. The reaction was diluted with 50 mL of  
25 ethylacetate, washed with water, brine, dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated to yield 62.5 mg of compound 38d.

Compound 38e: 3,5-dichloro-2-fluoro-4-[3-(phenethylamino-  
30 carbonyl)-4-hydroxyphenoxy]-6-hydroxycarbonyl methylamino pyridine



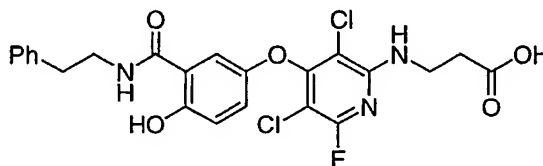
5           Compound 38d (62.5 mg) was dissolved in 1 mL of CH<sub>2</sub>Cl<sub>2</sub> under argon and cooled to -50°C. Boron tribromide (0.1mL) was added and the reaction mixture was stirred at ambient temperature for 4 hrs. The reaction mixture was diluted with 10 mL of methylene chloride, then quenched by the  
10 addition of 2g of cracked ice. MeOH was added and the reaction mixture was concentrated in vacuo. The crude reaction mixture was purified by preparative HPLC. The appropriate fractions were concentrated in vacuo to yield 22mg the title compound as a white solid.

15

<sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.27- 7.21(6 H, m), 7.05 (1H, dd, J3.30, 9.35 Hz), 3.56 (2H, t, J 7.15 Hz), 2.87 (2H, J7.70 Hz) [M+H]<sup>+</sup> 494

#### Example 39

20



25

**3,5-Dichloro-2-fluoro-4-[3-(phenethylamino-carbonyl)-4-hydroxyphenoxy]-6-hydroxycarbonyl ethylamino pyridine.**

30

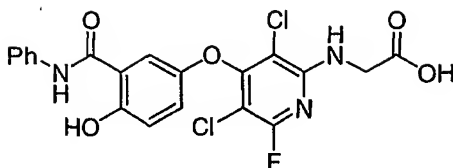
The title compound was prepared in the same manner as in Example 38. However, during the preparation of Compound 38d, β-alanine methyl ester HCl was substituted for glycine methyl ester HCl.

35

<sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.27-7.18 (6 H, m), 7.02 (1H, dd, J 2.63, 8.78 Hz), 2.87 (2H, t, J 7.03 Hz), 2.64 (2H, t, J 6.59 Hz). [M+H]<sup>+</sup> 509



5

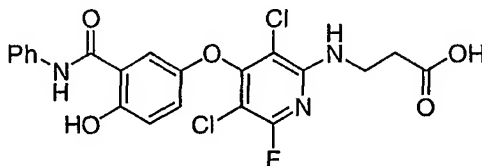
Example 40

10        **3,5-Dichloro-2-fluoro-4-[3-(phenylamino-carbonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethylamino pyridine**

          The title compound was prepared in the same manner as described in Example 38. However, during the preparation of  
15    Compound 38c, aniline was substituted for phenethylamine.

<sup>1</sup>H NMR(CD<sub>3</sub>OD) δ 7.61 (2H, d, J 8.35Hz), 7.53 (1H, d, J 3.07 Hz), 7.35 (2H, t, J 7.47), 7.15 (1H, t, 7.25), 7.09-7.06 (1H, m), 7.00-6.96 (1H, m). [M-H]<sup>-</sup> 464

20

Example 41

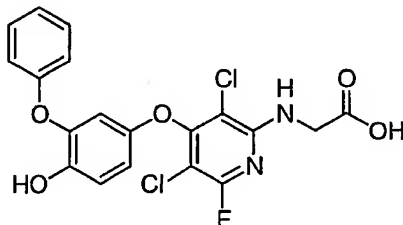
25        **3,5-Dichloro-2-fluoro-4-[3-(phenylamino-carbonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylethylamino pyridine**

          The title compound was prepared in the same manner as described in Example 38. However, during the preparation of  
30    Compound 38c and 38d, phenethylamine and glycine methyl ester were replaced by aniline and β-alanine methyl ester HCl respectively.

5  $^1\text{H}$  NMR( $\text{CD}_3\text{OD}$ )  $\delta$  7.61 (2H, d, J 8.25 Hz), 7.52 (1H, d, J 2.76 Hz), 7.35 (2H, t, 8.24 Hz), 7.15 (1H, 7.22 Hz), 7.06 (1H, dd, J 3.29, 9.35 Hz), 6.96 (1H, d, J 8.80 Hz)  $[\text{M}+\text{H}]^+$  480

Example 42

10



**3,5-Dichloro-2-fluoro-4-[3-(phenoxy)-4-hydroxyphenoxy]-6-hydroxycarbonylmethylaminopyridine**

15

Compound 42a: 3,5-Dichloro-2,6-difluoro-4-(3-hydroxy-4-methoxyphenoxy)pyridine

20 A solution of 3,5-Dichloro-2,6-difluoro-4-(3-formyl-4-methoxyphenoxy)pyridine (0.67g, 2mmol) and 70% MCPBA (0.64g, 2.6mmol) in 8ml of chloroform was stirred at room temperature overnight. The reaction mixture was diluted with 200 ml of ethyl acetate and washed with 5% aqueous sodiumhydrosulfite (4X), brine, dried ( $\text{Na}_2\text{SO}_4$ ), filtered and  
25 concentrated. The crude formate was dissolved in 20 ml of ethanol and 20 ml of 4N HCl in dioxane and stirred at room temperature for 2 hrs. The crude reaction mixture was concentrated, dissolved in methylene chloride (200ml) and  
30 washed with saturated aqueous  $\text{NaHCO}_3$  (3X), brine, dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated to provide compound 42a in 90% yield.

5  $^1\text{H}$ ( $\text{CDCl}_3$ ) 6.77 (1H, d J 8.80 Hz), 6.56 (1H, d J 2.75), 6.35 (1H, dd J 3.30 7.25), 3.88 (3H, s 3.88)

Compound 42b: 3,5-Dichloro-2,6-difluoro-4-(3-phenoxy-4-methoxyphenoxy)pyridine

10

3,5-Dichloro-2,6-difluoro-4-(3-hydroxy-4-methoxyphenoxy) pyridine (540mg, 1.7 mmol), phenylboronic acid (513 mg, 4.2 mmol), copper acetate (310mg, 1.7 mmol), pyridine (0.65ml), triethyl amine (0.98ml) and dried powdered molecular sieves (2g) were stirred as a slurry in 15 30 ml of methylene chloride overnight. The reaction mixture was filtered and the filtrate was concentrated to about 4ml. Product was purified by silica gel chromatography using 7% ethyl acetate in hexanes. The appropriate 20 fractions were combined and concentrated to give 440mg (64%) of compound 42b. M.P. 90-94C.

$^1\text{H}$  ( $\text{CDCl}_3$ ) 7.33 (2H, app t 8.2Hz), 7.10 (1H, t 7.4Hz), 6.97 (2H, d 7.7 Hz), 6.92 (1H, d 8.80), 6.64 (1H, d 2.75 Hz), 25 6.57 (1H, dd 3.30 9.08 Hz), 3.83 (3H s)

Compound 42c: 3,5-Dichloro-2-fluoro-4-(3-phenoxy-4-methoxyphenoxy)-6-methoxycarbonylmethylamino pyridine

30 Compound 42c was prepared in the same manner as described for compound 38d, except that 3,5-dichloro-2,6-difluoro-4-(3-phenoxy-4-methoxyphenoxy)pyridine was substituted for 3,5-dichloro-2,6-difluoro-4-[3-(phenethylaminocarbonyl)-4-methoxyphenoxy pyridine.

5 Compound 42c was obtained in 85% yield and was carried to the next step without further purification.

Compound 42d: 3,5-Dichloro-2-fluoro-4-(3-phenoxy-4-hydroxy-phenoxy)-6-hydroxycarbonylmethylaminopyridine

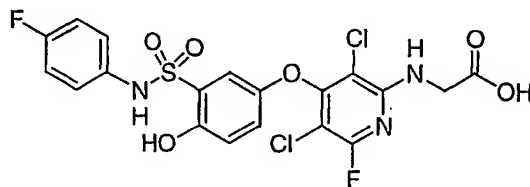
10

Compound 42d was prepared in the same manner as described for compound 38e.

$^1\text{H}$  ( $\text{CD}_3\text{OD}$ ) 7.31 (2H, app t 8.25 Hz), 7.05 (1H, t 7.70 Hz), 6.93 (2H, app d 7.70 Hz), 6.89 (1H, d 6.87 Hz), 6.55 (1H, dd 2.75 8.80 Hz), 6.48 (1H, d 2.75 Hz), 4.09 (2H, s)

15

#### Example 43



20

3,5-Dichloro-2-fluoro-4-[3-(parafluorophenaminosulfonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethylaminopyridine.

Compound 43a: 3,5-Dichloro-2,6-difluoro-4[3-(hydroxy-sulfonyl)-4-methoxyphenoxy]pyridine

25

3,5-Dichloro-2,6-difluoro-4-(4-methoxyphenoxy)pyridine (1.5g, 4.9 mmol) and chlorosulfonic acid (0.39 ml, 5.8 mmol) were stirred in 5 ml of methylene chloride overnight. The resulting solid was filtered and washed with cold

30  $\text{CH}_2\text{Cl}_2$ . Compound 43a was obtained as solid in 70% yield.

- 5     $^1\text{H}$  (DMSO- $d_6$ ) 7.36 (1H, d 3.51 Hz), 7.01-6.95 (2H, m), 3.75 (3H, s)

Compound 43b: 3,5-Dichloro-2,6-difluoro-4[3-(p-fluorophenyl-aminosulfonyl)-4-methoxyphenoxy]pyridine

- 10        Oxalyl chloride (2M in  $\text{CH}_2\text{Cl}_2$ , 0.2ml) was added to compound 43a (74.4 mg, 0.2 mmol, in 3 ml of  $\text{CH}_2\text{Cl}_2$  followed by the addition of catalytic DMF. The reaction was stirred at ambient temperature for 2 hrs. N-Methylmorpholine (.088ml, 0.8 mmol) was then added followed by the addition of 4-fluoroaniline (.076 ml, 0.8 mmol). The reaction
- 15    mixture was stirred overnight, diluted with methylene chloride, and washed with saturated aqueous  $\text{NaHCO}_3$ . The organic layer was dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. Compound 43b was purified by reverse phase preparative HPLC (42% yield).

- 20    Compound 43c: 3,5-Dichloro-2-fluoro-4-[3-(p-fluorophenyl-aminosulfonyl)-4-methoxyphenoxy]-6-methoxycarbonylmethyl-aminopyridine

- 3,5-Dichloro-2,6-difluoro-4[3-(p-fluorophenylaminosulfonyl)-4-methoxyphenoxy]pyridine (27.5 mg),
- 25    glycine methylester HCl (14.5 mg) and potassium carbonate (24 mg) were stirred at room temperature overnight. The reaction was diluted with 25 ml of methylene chloride, washed with water, brine, dried with  $\text{NaSO}_4$ , filtered and concentrated to yield 26.9 mg (85%) of compound 43c.

- 30    Compound 43d: 3,5-Dichloro-2fluoro-4[3-(p-fluorophenyl-aminosulfonyl)4-hydroxyphenoxy]-6-methoxycarbonyl-methylamino-pyridine

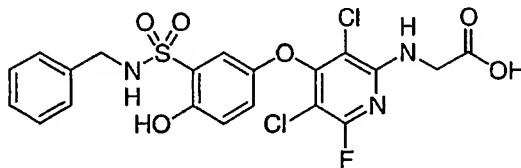
5           3,5-Dichloro-2fluoro-4-[3-(p-fluorophenylamino-sulfonyl)-4-methoxyphenoxy]pyridine (26.9 mg) was dissolved in 1 ml of methylene chloride and cooled to about -50°C under argon. Boron tribromide (0.05 ml) was added and the reaction was stirred at 0°C for 2 hrs. The reaction was  
10 diluted with 10ml of CH<sub>2</sub>Cl<sub>2</sub>, then quenched by the addition of about 1 g of cracked ice. MeOH (5 ml) was added and the reaction was concentrated in vacuo. The concentration from methanol was repeated 2X more.

Compound 43e: 3,5-Dichloro-2-fluoro-4-[3-(p-fluorophenyl-  
15 aminosulfonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylamino-methylpyridine

3,5-Dichloro-2-fluoro-4[3-(p-fluorophenyl-aminosulfonyl)-4-hydroxyphenoxy]6-methoxycarbonyl methyl-  
20 aminopyridine was stirred for 2 hours at room temperature in 2ml of THF and 0.5 ml of 1N LiOH. The reaction was acidified to pH 2 with dilute aqueous TFA. The reaction was concentrated to remove THF then purified by reverse phase preparative HPLC. The appropriate fractions were combined and concentrated to yield 18.8 mg (73% from  
25 compound 43c) of compound 43e for 2 steps.

<sup>1</sup>H (CD<sub>3</sub>OD) 7.90-6.90 (7H, m), 4.12 (2H, s) [M-H]<sup>-</sup> 518

Example 44



30

5

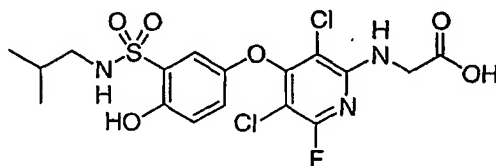
**3,5-Dichloro-2-fluoro-4-[3-(benzylaminosulfonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethylaminopyridine.**

The title compound was prepared according to the methodology described for example 43 except that benzyl amine was used in place of 4-fluoroaniline in the step for compound 43b.

$^1\text{H}$  ( $\text{CD}_3\text{OD}$ ) 7.21-7.17 (6H, m), 7.01 (1H, dd 2.75Hz, 9.07Hz), 6.86 (1H, d 9.34Hz), 4.12 (1H, s), 4.09 (1H, s)  $[\text{M}-\text{H}]^-$  514

15

Example 45

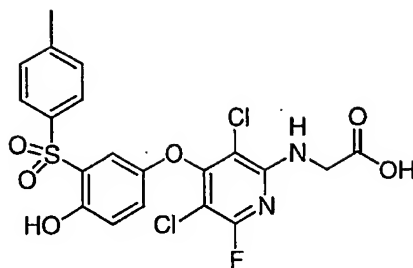


**3,5-Dichloro-2-fluoro-4-[3-(isobutylaminosulfonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethylaminopyridine.**

The title compound was prepared according to the methodology described for example 43 except that isobutyl amine was used in place of 4-fluoroaniline in the step for compound 43b.

$^1\text{H}$  ( $\text{CD}_3\text{OD}$ ) 7.18 (1H, d 3.30Hz), 7.09 (1H, dd 3.30Hz, 8.80Hz), 6.97 (1H, d 9.34Hz), 4.12 (2H, s), 2.66 (2H, d 6.60Hz), 1.69-1.65 (1H, m), 0.85 (6H, d 6.60Hz)  $[\text{M}-\text{H}]^-$  480

Example 46



5

**3,5-Dichloro-2-fluoro-4-[3-(p-tolylsulfonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethylaminopyridine.**

10

Compound 46a: 3,5-Dichloro-2,6-difluoro-4[3-(p-tolylsulfonyl)-4-hydroxyphenoxy]pyridine

3,5-Dichloro-2,6-difluoro-4-(4-methoxyphenoxy)pyridine  
 (0.3 g, 1 mmol), tosylchloride (0.2 g, 1 mmol) and aluminum  
 chloride (0.29 g, 2.1 mmol) were heated at 70°C for 14 hrs  
 in 15 ml of dichloroethane. The reaction mixture was  
 diluted with 50ml additional dichloroethane, cooled to 0°C  
 and quenched by the addition of 1 ml of water. After  
 stirring for 5 minutes, the organic layer was separated,  
 washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated. The  
 crude material was purified by silica chromatography to  
 give a 47% yield of compound 46a.

<sup>1</sup>H (CDCl<sub>3</sub>) 8.90 (1H, s), 7.72 (2H, d 8.14Hz), 7.27 (2H, d 8.24Hz), 7.09 (1H, d 3.29 Hz), 6.98-6.91 (2H, m), 2.36 (3H, s)

Compound 46b: 3,5-Dichloro-2-fluoro-4-[3-(p-tolylsulfonyl)-4-hydroxyphenoxy]-6-methoxycarbonylaminomethylpyridine

30



5           Compound 46b was prepared according to the method described for compound 43c.

Compound 46c: 3,5-Dichloro-2-fluoro-4-[3-(p-tolylsulfonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylaminomethylpyridine

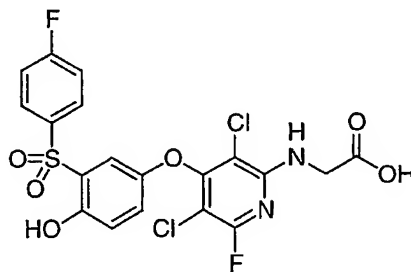
10

          Compound 46c was prepared according to the methodology described for compound 43e.

<sup>1</sup>H (CD<sub>3</sub>OD) 7.81 (2H, d 7.91Hz), 7.41 (1H, d 3.08Hz), 7.35 (2H, d 7.91Hz), 7.07 (1H, dd 3.08, 8.29) 4.12 (2H, s), 2.41 (3H, s)

15

Example 47



**3,5-Dichloro-2-fluoro-4-[3-(p-fluorobenzenesulfonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylmethylaminopyridine.**

25 Compound 47a: 2-(4-Fluorobenzenesulfonyl)-benzene-1,4-diol

          To a solution (50 ml THF) of 4-Fluorobenzenesulfonyl chloride (2 g) was added sodiumborohydride (1.9 g) and the reaction was stirred for 1 hour. The reaction was quenched with 5 ml of water and after stirring for 1 hour was concentrated. Ten ml of 6N HCl was added dropwise and 4-

30

5 fluorobenzenesulfinic acid was extracted with ethyl acetate. The ethyl acetate solution was dried with  $\text{Na}_2\text{SO}_4$ , filtered and concentrated. The resulting residue was dissolved in 5 ml of water and was added dropwise to a methylene chloride solution of 1,4-benzoquinone. The  
10 reaction mixture was stirred over night. Compound 47a was filtered and dried to yeild 1.8 g (72%).

Compound 47b: 3,5 Dichloro-2,6-difluoro-4-[3-(p-fluoro-sulfonyl)-4-hydroxyphenoxy]pyridine

15

2,4,6-trifluoro-3,5-dichloropyridine (20.1 mg), 2-(4-fluorobenzenesulfonyl)-benzene-1,4-diol (26.8 mg) and triethylamine (5  $\mu\text{l}$ ) were stirred in 1 ml of dimethylformamide overnight. The reaction mixture was  
20 concentrated and the crude product purified on a preparative silica gel plate to yield 14 mg of compound 47b.

Compound 47c: 3,5 Dichloro-2,6-difluoro-4-[3-(p-fluoro-sulfonyl)-4-hydroxyphenoxy]-6-methoxycarbonylaminomethyl  
25 pyridine

Compound 47c was prepared according to the procedure described for compound 43c.

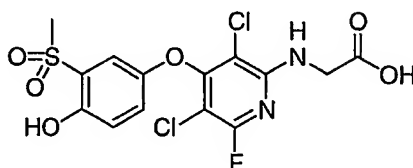
30

Compound 47d: 3,5-Dichloro-2-fluoro-4-[3-(p-fluorobenzene-sulfonyl)-4-hydroxyphenoxy]-6-hydroxycarbonylaminomethyl pyridine

5           Compound 47d was prepared according to the procedure described for compound 43e.

$^1\text{H}$  ( $\text{CD}_3\text{OD}$ ) 8.04-8.00 (2H, m), 7.47 (1H, d 3.30Hz), 7.32-7.27 (2H, m), 7.09 (1H, dd 3.30Hz, 9.07 Hz), 6.86 (1H, d 8.80Hz),  
10 4.13 (2H, s) (M-H) $^-$  503

Example 48



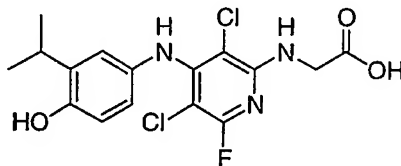
15

**3,5-Dichloro-2-fluoro-4-(3-methanesulfonyl-4-hydroxyphenoxy)-6-hydroxycarbonylmethylaminopyridine.**

The title compound was prepared according to the  
20 procedures described for example 47 except that 2-methylsulfonyl-benzene-1,4-diol was prepared from Na methanesulfinate and 1,4-benzoquinone.

$^1\text{H}$  ( $\text{CD}_3\text{OD}$ ) 7.30 (1H, d 3.30Hz), 7.13 (1H, dd 3.30Hz, 8.80  
25 Hz), 7.00 (1H, d 9.35Hz), 4.09 (2H, s), 3.25 (3H, s)

Example 49

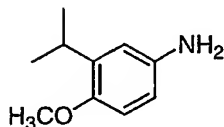


30

**3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenylamino)-6-hydroxycarbonylmethylaminopyridine.**

5

Compound 49a: 3-isopropyl-4-methoxyaniline



10 To a solution of 2-isopropylanisole (0.4 g, 2.66 mmol) in  $\text{CH}_2\text{Cl}_2$  (13 mL) was added bis-(2,2,2-trichloroethyl)azo-dicarboxylate (2.3 g, 6.04 mmol) and zinc chloride (3 mL, 1.0 M solution in  $\text{Et}_2\text{O}$ , 3.0 mmol). The mixture was left to stir overnight (ca. 18h) at ambient room temperature under

15  $\text{N}_2$ . A 25% aqueous ammonium acetate solution (15 mL) was added to quench the reaction. The product was extracted with EtOAc (50 mL). The EtOAc extract was washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The thick yellow oil crude product was purified by

20 chromatography using the ISCO Combiflash SQ16x system (0 to 50% EtOAc in hexane, 15 min gradient, 35 g Redisep silica gel column) to afford 1.75 g of material which was a mixture of two products. The mixture was dissolved in glacial acetic acid (10 mL). Zinc dust (1 g) was added and

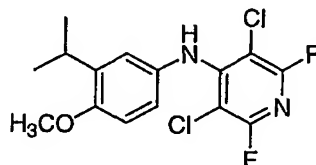
25 the reaction mixture was left to stir overnight (ca. 15 h) under  $\text{N}_2$  at ambient room temperature. The reaction was quenched by adding 3 N HCl to dissolve the remaining zinc dust. Water (50 mL) and 50% aqueous NaOH was added to make the mixture basic (ca. pH 10). The product was extracted

30 with EtOAc (100 mL). The EtOAc extract was washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude product was purified by chromatography using the ISCO Combiflash SQ16x system ( 0 to 50% EtOAc in

5 hexane, 15 min gradient, 35 g Redisep silica gel column) to afford 0.343 g (78%, 2 steps) of compound 49a as a purified orange oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 6.68 (d, 1H, J = 8.8 Hz), 6.595  
10 (d, 1H, J = 2.8 Hz), 6.495 (dd, 1H, J = 8.2, 2.7 Hz), 3.75 (s, 3H), 3.29 (broad s, 2H), 3.25 (m, 1H), 1.17 (d, 6H, J = 7.2 Hz) MS-ESI [M+H]<sup>+</sup> = 166.2

Compound 49b: 3,5-dichloro-2,6-difluoro-4-(3-isopropyl-4-methoxyphenylamino)pyridine  
15



To a stirring slurry of 4-amino-2-isopropylanisole (0.150 g, 0.908 mmol) and K<sub>2</sub>CO<sub>3</sub> (0.150g, 1.085 mmol) in DMF  
20 (3 mL) was added a solution of 3,5 dichloro-2,4,6-trifluoropyridine (0.185 g, 0.916 mmol) in DMF (1.5 mL). The mixture was stirred at ambient room temperature for 2 h. The mixture was partitioned between EtOAc (50 mL) and H<sub>2</sub>O (25 mL). The EtOAc extract was washed with brine (25  
25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by chromatography using the ISCO Combiflash SQ16x system (0 to 15% EtOAc in hexane, 15 min gradient, 35 g Redisep silica gel column) to afford 0.279 g (88%) of compound 49b as a purified white solid.

30

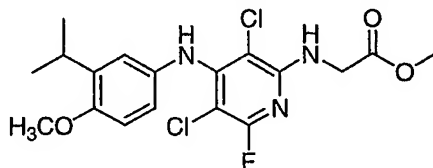
<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 6.92 (d, 1H, J = 2.2 Hz), 6.875 (dd, 1H, J = 8.2, 2.7 Hz), 6.80 (broad s, 1H), 6.78 (d, 1H,

5 J = 8.8 Hz), 3.84 (s, 3H), 3.31 (m, 1H), 1.175 (d, 6H, J = 7.1 Hz)

MS-ESI [M-H]<sup>-</sup> = 345.1, 347.1, 348.1 (100:64:10)

Compound 49c: 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenylamino)-6-methoxycarbonylmethylaminopyridine

10



To a solution of compound 49b (0.150 g, 0.432 mmol) and glycine methyl ester hydrochloride (0.160 g, 1.274 mmol) in DMF (4 mL) was added N,N-diisopropylethylamine (0.35 mL, 0.26 g, 2.012 mmol). The mixture was heated to 70°C and maintained at this temperature overnight (ca. 15 h) under N<sub>2</sub>. The mixture was cooled down to room temperature and then taken up in EtOAc (50 mL) and H<sub>2</sub>O (25 mL). The EtOAc extract was washed with brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by chromatography using the ISCO Combiflash SQ16x system (0 to 50% EtOAc in hexane, 15 min gradient, 35 g Redisep silica gel column) to afford 0.065 g of compound 49c (48036-110B) as a white solid.

15

20

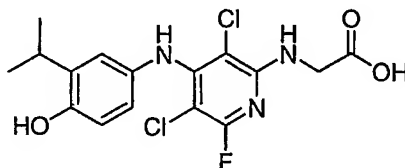
25

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 6.865 (d, 1H, J = 2.2 Hz), 6.785 (dd, 1H, J = 8.8, 2.2 Hz), 6.75 (d, 1H, J = 8.8 Hz), 6.36 (broad s, 1H), 5.49 (t, 1H, J = 5 Hz), 4.19 (d, 2H, J = 5.5 Hz), 3.82 (s, 3H), 3.78 (s, 3H), 3.29 (m, 1H), 1.175 (d, 6H, J = 7.2 Hz)

30

MS-ESI [M-H]<sup>-</sup> = 414.2, 416.2, 418.2 (100:64:10)

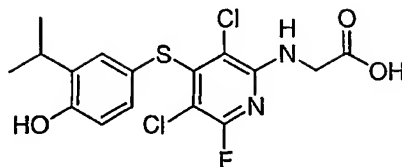
- 5 Compound 49d: 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenylamino)-6-hydroxycarbonylmethylaminopyridine



- 10 To a solution of compound 49c (55 mg, 0.132 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) cooled with an ice- $\text{H}_2\text{O}$  bath was added boron tribromide (1.3 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 1.3 mmol). The temperature was allowed to warm up to room temperature. After 2 h, the mixture was poured into a flask containing  
15 ice-water (25 mL) and stirred for 10 min. The product was extracted with EtOAc (25 mL). The EtOAc extract was washed with brine (25 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude product was purified by prep HPLC to afford 37.6 mg (73%) of title compound as an  
20 orange solid.

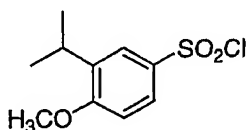
- $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ) 6.80 (d, 1H,  $J = 2.2$  Hz), 6.64 (s, 1H), 6.635 (d, 1H,  $J = 2.2$  Hz), 2.06 (s, 2H), 3.24 (m, 1H), 1.17 (d, 6H,  $J = 6.6$  Hz)  
25 MS-ESI  $[\text{M}-\text{H}]^- = 386.1, 388.1, 390.1$  (100:64:10)

5

Example 50

10 **3,5-Dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenylthio)-6-hydroxycarbonylmethylaminopyridine**

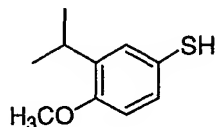
Compound 50a: 4-chlorosulfonyl-2-isopropylanisole



To a solution of 2-isopropylanisole (0.40 g, 2.66  
 15 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (9 mL) cooled with an ice water bath was added slowly chlorosulfonic acid (4 mL). After 1.5 h of cooling, the mixture was poured into a flask containing ice (25 g). The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The organic extract was washed with brine (25 mL), dried  
 20 (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo to afford 0.62 g of grayish oil as crude product. The crude product was purified by chromatography using the ISCO Combiflash SQ16x system (0 to 20% EtOAc in hexane, 20 min gradient, 35 g Redisep silica gel column) to give 0.56 g (84%) of compound  
 25 50a as a clear oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 7.87 (dd, 1H, J = 8.8 Hz, 2.2 Hz),  
 7.82 (d, 1H, J = 2.8 Hz), 6.96 (d, 1H, J = 8.8 Hz), 3.94 (s,  
 3H), 3.33 (m, 1H), 1.235 (d, 6H, J = 6.6 Hz)  
 30 MS-DCI<sup>+</sup> [M-Cl]<sup>+</sup> = 212.8 (100%)

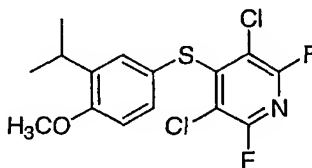


5 Compound 50b: 4-thio-2-isopropylanisole

A mixture of 4-chlorosulfonyl-2-isopropylanisole (0.30  
10 g, 1.21 mmol), zinc dust (0.5 g) in 25% H<sub>2</sub>SO<sub>4</sub> (15 mL) was  
heated to 110°C and maintained at this temperature for 4 h.  
The mixture was cooled down to RT and the product was  
extracted with EtOAc (50 mL). The EtOAc extract was washed  
with brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and  
15 concentrated and dried in vacuo to give 0.18 g (82%) of  
compound 50b.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 7.165 (d, 1H, J = 2.2 Hz), 7.135  
(dd, 1H, J = 8.2 Hz, 2.2 Hz), 6.72 (d, 1H, J = 8.8 Hz), 3.79  
20 (s, 3H), 3.25 (m, 1H), 1.17 5 (d, 6H, J = 6.6 Hz)

Compound 50c: 3,5-dichloro-2,6-difluoro-4-(3-isopropyl-4-methoxyphenylthio) pyridine

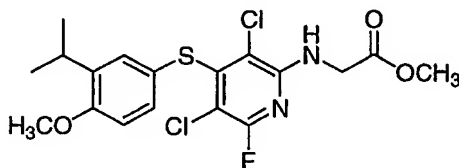


25 To the crude 4-thio-2-isopropylanisole (0.14 g, 0.77  
mmol) in DMF (3 mL) was added potassium carbonate (0.17 g,  
1.23 mmol) and a solution of 3,5-dichloro-2,4,6-  
trifluoropyridine (0.14 g, 0.69 mmol) in DMF (1 mL). After  
2h, the mixture was partitioned between EtOAc (50 mL) and  
30 H<sub>2</sub>O (25 mL). The EtOAc extract was washed with brine (25

5 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude product was purified by chromatography (50 g silica gel, 2% EtOAc in hexane) to afford 0.18 g (64%) of compound 50c.

10  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.29 (d, 1H,  $J = 2.2$  Hz), 7.135 (dd, 1H,  $J = 8.5$  Hz, 2.2 Hz), 6.76 (d, 1H,  $J = 8.8$  Hz), 3.82 (s, 3H), 3.26 (m, 1H), 1.16 (d, 6H,  $J = 6.6$  Hz)

Compound 50d: 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-methoxyphenylthio)-6-methoxycarbonylmethylaminopyridine  
15

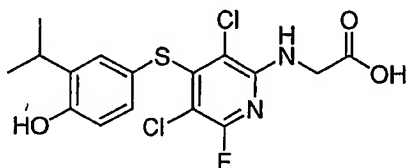


To a solution of compound 50c (0.17 g, 0.47 mmol) and  
20 glycine methyl ester hydrochloride (0.12 g, 0.95 mmol) in  
N, N-dimethylacetamide (5 mL) was added N,N-  
diisopropylethyl-amine (0.35 mL, 0.26g, 2.01 mmol). The  
mixture was heated to 70°C and maintained at this  
temperature for 3 h. The mixture was cooled to RT and  
25 partitioned between EtOAc (50 mL) and  $\text{H}_2\text{O}$  (25 mL). The  
EtOAc extract was washed with 1N HCl (25 mL) and brine (25  
mL) and then dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in  
vacuo. The crude product was purified by chromatography  
(50 g silica gel, 15% EtOAc in hexane) to afford 0.15 g  
30 (72%) of compound 50d as a white solid.

5  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.29 (d, 1H,  $J = 2.6$  Hz), 7.15 (dd, 1H,  $J = 8.6$  Hz, 2.4 Hz), 6.73 (d, 1H,  $J = 8.4$  Hz), 5.71 (t, 1H,  $J = 4.8$  Hz), 4.17 (d, 2H,  $J = 5.3$  Hz), 3.79 (s, 3H), 3.78 (s, 3H), 3.24 (m, 1H), 1.16 (d, 6H,  $J = 7.1$  Hz)  
MS-ESI $^-$   $[\text{M}-\text{H}]^- = 431, 433, 435$  (100:64:10)

10

Compound 50e: 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenylthio)-6-hydroxycarbonylmethylaminopyridine

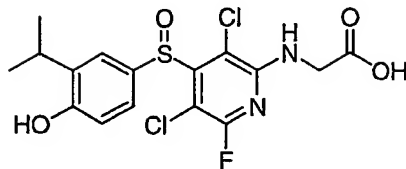


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To a solution of 48036-163 (65 mg, 0.15 mmol) in  $\text{CH}_2\text{Cl}_2$  (3 mL) cooled with an ice water bath was added boron tribromide (1.0 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 1.0 mmol). The temperature was allowed to warm up to room temperature.  
20 After 2 h, the mixture was poured into a flask containing ice-water (25 mL) and stirred for 10 min. The product was extracted with EtOAc (50 mL). The EtOAc extract was washed with brine (25 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude product was purified by  
25 prep HPLC to afford 29 mg (48%) of the title compound as a white solid.

$^1\text{H}$  NMR (400 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ) 7.20 (d, 1H,  $J = 2.7$  Hz), 6.995 (dd, 1H,  $J = 8.4$  Hz, 2.7 Hz), 6.68 (d, 1H,  $J = 8.4$  Hz), 4.07 (s, 2H), 3.21 (m, 1H), 1.155 (d, 6H,  $J = 7.0$  Hz)  
30 MS-ESI $^-$   $[\text{M}-\text{H}]^- = 403, 405, 407$  (100:64:10)

5

Example 51

10 **[3,5-Dichloro-6-fluoro-4-(4-hydroxy-3-isopropylbenzenesulfinyl)pyridin-2-ylamino]acetic acid**

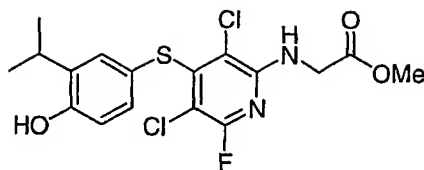
To a solution of 3,5-dichloro-2-fluoro-4-(3-isopropyl-4-hydroxyphenylthio)-6-hydroxycarbonylmethylaminopyridine (25 mg, 0.06 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL) was added 3-chloroperoxybenzoic acid (11 mg). The mixture was left to stir overnight (ca. 15h) at ambient room temperature. The product was extracted with EtOAc (25 mL). The organic extract was washed with brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The isolated crude product was purified by preparative HPLC (from 50% B to 100% B for 10 min, Solvent A = 90% H<sub>2</sub>O-10% MeOH-0.1% TFA, Solvent B = 10% MeOH-90% H<sub>2</sub>O-0.1% TFA, at 20 mL/min using column YMC ODS S5 20 x 100 mm) to afford 16.5 mg (64%) of title compound as a white solid.

25

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, δ) 7.70 (d, 1H, J = 2.2 Hz), 7.435 (dd, 1H, J = 8.8 Hz, 2.2 Hz), 6.89 (d, 1H, J = 8.4 Hz), 4.08 (s, 2H), 3.71 (s, 3H), 3.32-3.37 (m, 1H), 1.21, 1.20 (2d, 6H, J = 7.0 Hz)

30 MS-ESI<sup>-</sup> [M-H]<sup>-</sup> = 419, 421, 423 (100:64:10)

Example 52



5

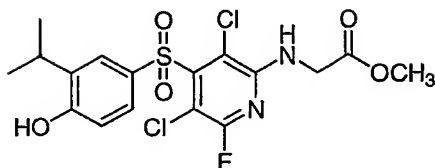
**[3,5-Dichloro-6-fluoro-4-(4-hydroxy-3-isopropyl-benzene-sulfanyl)pyridin-2-ylamino]acetic acid methyl ester**

10 To a solution of [3,5-dichloro-6-fluoro-4-(3-isopropyl-4-methoxy-phenylsulfanyl)-pyridin-2-ylamino]-acetic acid methyl ester (600 mg, 1.38 mmol) in  $\text{CH}_2\text{Cl}_2$  (14 mL) cooled with an ice water bath was added boron tribromide (0.65 mL, 1.72 g, 6.87 mmol). The temperature  
15 was allowed to warm up to RT. After 2 h, the mixture was slowly poured into a flask containing EtOAc (100 mL) and saturated aqueous  $\text{NaHCO}_3$  solution (75 mL). The EtOAc extract was washed with brine (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated in vacuo. The crude product was  
20 refluxed in methanolic HCl (30 mL) for 2 h. The temperature was cooled to room temperature and then concentrated in vacuo. The crude product was purified by chromatography using the ISCO Combiflash SQ16X system (35 g Redisepp silica gel column, 0 to 50% EtOAc in hexane for 30  
25 min at 30 mL/min) to afford 517.4 mg (89%) of the title compound as a yellowish thick oil.

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.30 (d, 1H,  $J = 2.2$  Hz), 7.045 (dd, 1H,  $J = 8.2$  Hz, 2.2 Hz), 6.65 (d, 1H,  $J = 8.8$  Hz), 5.71 (t, 1H,  $J = 5.0$  Hz), 4.86 (s, 1H), 4.175 (d, 2H,  $J = 5.0$  Hz), 3.78 (s, 3H), 3.18-3.11 (m, 1H), 1.21 (d, 6H,  $J = 7.2$  Hz)

MS-ESI $^-$   $[\text{M}-\text{H}]^- = 417, 419, 421$  (100:64:10)

5

Example 53

10      **[3,5-Dichloro-6-fluoro-4-(4-hydroxy-3-isopropyl-benzenesulfonyl)pyridin-2-ylamino]acetic acid methyl ester**

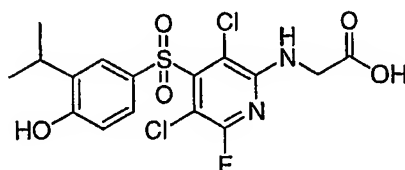
To a solution of [3,5-dichloro-6-fluoro-4-(4-hydroxy-3-isopropyl-benzenesulfonyl)pyridin-2-ylamino]acetic acid methyl ester (title compound of example 52) (175 mg, 0.42 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) was added 3-chloroperoxybenzoic acid (300 mg). The mixture was left to stir overnight (ca. 15h) at ambient room temperature. The mixture was poured into a flask containing saturated aqueous NaHCO<sub>3</sub> (50 mL). The product was extracted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The organic extract was washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by chromatography using the ISCO Combiflash SQ16X system (35 g Redisep silica gel column, 0 to 75% EtOAc in hexane for 20 min at 30 mL/min) to afford 167.3 mg (89%) of desired product as a white solid which was 92% pure by analytical HPLC. The product isolated was further purified by preparative HPLC (from 50% B to 100% B for 10 min, Solvent A = 90% H<sub>2</sub>O-10% MeOH-0.1% TFA Solvent B = 10% MeOH-90% H<sub>2</sub>O-0.1% TFA, at 20 mL/min using column YMC ODS S5 20 x 100 mm) to afford 90 mg of the title compound as a white solid.

5

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ) 7.88 (d, 1H,  $J = 2.8$  Hz), 7.73 (dd, 1H,  $J = 8.8$  Hz, 2.2 Hz), 6.65 (d, 1H,  $J = 8.8$  Hz), 4.11 (s, 2H), 3.71 (s, 3H), 3.33-3.28 (m, 1H), 1.22 (d, 6H,  $J = 7.1$  Hz)

10 MS-ESI $^-$   $[\text{M}-\text{H}]^- = 449, 451, 453$  (100:64:10)

Example 54



15

**[3,5-Dichloro-6-fluoro-4-(4-hydroxy-3-isopropyl-benzene-sulfonyl)pyridin-2-ylamino]acetic acid**

To a solution of the title compound of example 53 (90 mg, 0.20 mmol) in THF (2 mL) was added 1N LiOH aqueous solution (0.6 mL). After an hour, the mixture was acidified with 1N HCl and the product was extracted with EtOAc (50 mL). The organic extract was washed with brine (20 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered and concentrated and dried in vacuo to afford 77.4 mg (89%) of the title compound as a white solid.

20

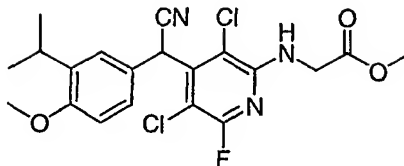
25

$^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ ,  $\delta$ ) 7.88 (d, 1H,  $J = 2.2$  Hz), 7.73 (dd, 1H,  $J = 8.8$  Hz, 2.2 Hz), 6.91 (d, 1H,  $J = 8.2$  Hz), 4.07 (s, 2H), 3.71 (s, 3H), 3.32-3.27 (m, 1H), 1.22 (d, 6H,  $J = 7.1$  Hz)

30

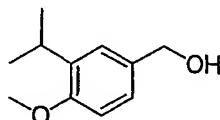
MS-ESI $^-$   $[\text{M}-\text{H}]^- = 435, 437, 439$  (100:64:10)

5

Example 55

10       **{3,5-dichloro-4-[cyano-(3-isopropyl-4-methoxy-phenyl)-methyl]-6-fluoro-pyridin-2-ylamino}-acetic acid methyl ester**

Compound 55a: (3-Isopropyl-4-methoxyphenyl)methanol



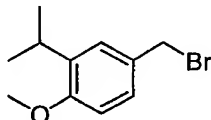
15       To a solution of 3-isopropyl-4-methoxy-benzaldehyde (1.5 g, 8.42 mmol) in anhydrous THF (17 mL) cooled to -78°C with a dry ice-acetone bath was added diisobutylaluminum hydride (34 mL, 1.0 M solution in THF, 34 mmol). After 1.5 h of cooling, 1N HCl (30 mL) was slowly added to the  
20       mixture. After the addition, the cooling bath was removed and the mixture left to stir at RT (ca. 15 min). The product was extracted with EtOAc (100 mL). The EtOAc extract was washed with brine (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo to give 1.405 g of  
25       colorless oil as crude product. The crude product was purified by chromatography using the ISCO Combiflash SQ16X system (35 g Redisep silica gel column, 0 to 40% EtOAc in hexane for 30 min at 30 mL/min) to afford 1.272 g (84%) of compound 55 as a colorless oil.

30



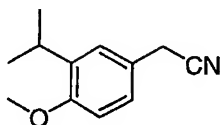
5  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.21 (d, 1H,  $J = 2.2$  Hz), 7.16 (dd, 1H,  $J = 8.3, 2.2$  Hz), 6.825 (d, 1H,  $J = 8.3$  Hz), 4.61 (d, 2H,  $J = 6.1$  Hz), 3.82 (s, 3H), 3.31 (heptet, 1H, 6.6 Hz), 1.50 (t, 1H,  $J = 5.8$  Hz), 1.205 (d, 6H,  $J = 7.1$  Hz)

10 Compound 55b: 4-Bromomethyl-2-isopropyl-1-methoxybenzene



To a solution of (3-isopropyl-4-methoxy-phenyl)-methanol (0.400g, 2.219 mmol) in  $\text{CH}_2\text{Cl}_2$  (4.5 mL) was added  
15 phosphorus tribromide (2.3 mL, 1.0 M solution in  $\text{CH}_2\text{Cl}_2$ , 2.300 mmol). After 2h,  $\text{H}_2\text{O}$  (25 mL) was added to quench the mixture. The product was extracted with  $\text{CH}_2\text{Cl}_2$  (50 mL). The organic extract was washed succesively with saturated  $\text{NaHCO}_3$  solution (2 x 25 mL) and brine (25 mL). The organic  
20 extract was dried ( $\text{Na}_2\text{SO}_4$ ), filtered, concentrated and dried in vacuo to afford 0.5294 mg (98% crude yield) of compound 55b as a colorless oil.

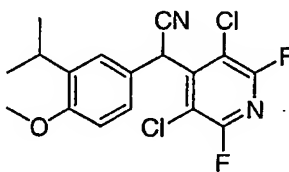
$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ,  $\delta$ ) 7.215 (d, 1H,  $J = 2.2$  Hz), 7.195  
25 (dd, 1H,  $J = 8.2, 2.2$  Hz), 6.785 (d, 1H,  $J = 8.3$  Hz), 4.51 (s, 2H), 3.82 (s, 3H), 3.28 (heptet, 1H, 7.1 Hz), 1.20 (d, 6H,  $J = 6.6$  Hz)

5 Compound 55c: (3-Isopropyl-4-methoxyphenyl)acetonitrile:

Sodium cyanide (0.500 g, 10.202 mmol) in DMSO (4 mL) was heated to 100°C. After a few minutes of heating, most of the sodium cyanide was dissolved. A solution of the crude 4-bromoethyl-2-isopropyl-1-methoxy-benzene (0.500 g, 2.065 mmol) in DMSO (1.5 mL) was added to the sodium cyanide solution. After an hour of heating, the mixture was cooled to RT and the product partitioned between EtOAc (100 mL) and H<sub>2</sub>O (50 mL). The EtOAc extract was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude product was purified by chromatography using the ISCO Combiflash SQ16X system (35 g Redisep silica gel column, 0 to 20% EtOAc in hexane for 20 min at 30 mL/min) to afford 0.326 g (84%) of compound 55c as a colorless oil.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 7.11 (dd, 1H, J = 6.5, 2.7 Hz), 7.10 (s, 1H), 6.815 (dd, 1H, J = 6.6, 2.8 Hz), 3.82 (s, 3H), 3.67 (s, 2H), 3.29 (heptet, 1H, 6.6 Hz), 1.195 (d, 6H, J = 6.6 Hz)

MS-DCI : [M-H]<sup>+</sup> 188.2

Compound 55d: (3,5-dichloro-2,6-difluoro-pyridin-4-yl)-(3-isopropyl-4-methoxyphenyl)acetonitrile

5

To a stirring slurry of sodium hydride (30 mg, 60% dispersion, 0.75 mmol) in DMF (1 mL) was added a solution of (3-isopropyl-4-methoxy-phenyl)-acetonitrile (70 mg, 0.37 mmol) in DMF (1 mL). The mixture was stirred for ca. 10 min, then a solution of 3,5-dichloro-2,4,6-trifluoropyridine in DMF (1.5 mL) was added. After 2h, the mixture was quenched with H<sub>2</sub>O (10 mL) and the product was extracted with EtOAc (50 mL). The EtOAc extract was washed with brine, dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo. The crude product was purified by preparative HPLC (from 50% B to 100% B for 10 min, Solvent A = 90% H<sub>2</sub>O-10% MeOH-0.1% TFA Solvent B = 10% MeOH-90% H<sub>2</sub>O-0.1% TFA, at 20 mL/min using column YMC ODS S5 20 x 100 mm) to afford 59.3 mg (43%) of compound 55d as a white solid.

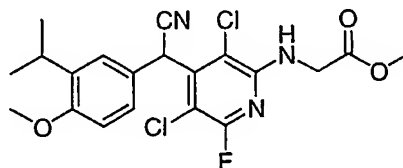
20

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 7.25 (d, 1H, J = 2.7 Hz), 7.095 (dd, 1H, J = 7.7 2.8 Hz), 6.80 (d, 1H, J = 8.8 Hz), 6.11 (s, 1H), 3.81 (s, 3H), 3.27 (heptet, 1H, 7.1 Hz), 1.185, 1.16 (2d, 6H, J = 6.6 H, 7.2 Hz)

25 MS-ESI : [M-H]<sup>-</sup> 369, 371, 373 (100:64:10)

Compound 55e: {3,5,dichloro-4-[cyano-(3-isopropyl-4-methoxy-phenyl)-methyl]-6-fluoropyridin-2-ylamino}acetic acid methyl ester

30



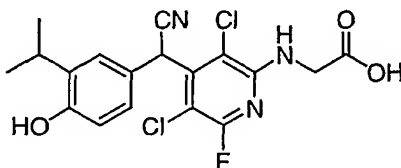
5 A mixture of (3,5-dichloro-2,6-difluoro-pyridin-4-yl)-  
(3-isopropyl-4-methoxy-phenyl)-acetonitrile (55 mg, 0.148  
mmol), glycine methyl ester hydrochloride (40 mg, 0.19  
mmol) and *N,N*-disopropylethylamine (89 mg, 0.12 mL, 0.689  
mmol) in *N,N*-dimethylacetamide (3 mL) was heated to 70°C and  
10 maintained at this temperature for an hour. The mixture  
was cooled to room temperature and diluted with EtOAc (75  
mL). Subsequently, the mixture was washed successively  
with 1N HCl (2 x 50 mL) and brine (50 mL), then dried  
(Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude  
15 product was purified by chromatography using the ISCO  
Combiflash SQ16X system (35 g Redisep silica gel column, 0  
to 60% EtOAc in hexane for 30 min at 30 mL/min) to afford  
56.2 mg (86%) of compound 55e as a white solid.

20 <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, δ) 7.265 (d, 1H, *J* = 2.7 Hz), 7.095  
(dd, 1H, *J* = 7.7, 2.7 Hz), 6.78 (d, 1H, *J* = 8.2 Hz), 6.02  
(s, 1H), 5.79 (t, 1H, *J* = 5.0 Hz), 4.185 (d, 2H, *J* = 5.5  
Hz), 3.80 (s, 3H), 3.79 (s, 3H), 3.27 (heptet, 1H, 6.6 Hz),  
1.19, 1.165 (2d, 6H, *J* = 6.6, 6.6 Hz).

25 MS ESI<sup>-</sup> [M-H]<sup>-</sup> : 438, 440, 442 (100:64:10)

#### Example 56

30 {3,5-dichloro-4-[cyano-(4-hydroxy-3-isopropylphenyl)-  
methyl]-6-fluoropyridin-2-ylamino}acetic acid



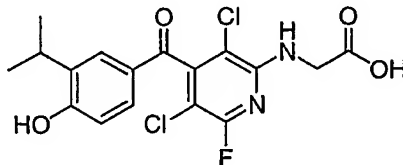
5 To a solution of {3,5-dichloro-4-[cyano-(3-isopropyl-  
4-methoxy-phenyl)-methyl]-6-fluoro-pyridin-2-ylamino}-  
acetic acid methyl ester (35 mg, 0.08 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL)  
cooled with an ice-water bath was added boron tribromide  
(1.0 mL, 1.0 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 1.0 mmol). The  
10 temperature was allowed to warm up to RT. After 2 h, the  
mixture was poured into a flask containing ice water (25  
mL). The product was extracted with EtOAc (50 mL). The  
organic extract was washed with brine (25 mL), dried  
(Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo. The crude  
15 product isolated was purified by preparative HPLC (from 50%  
B to 100% B for 10 min, Solvent A = 90% H<sub>2</sub>O-10% MeOH-0.1%  
TFA Solvent B = 10% MeOH-90% H<sub>2</sub>O-0.1% TFA, at 20 mL/min  
using column YMC ODS S5 20 x 100 mm) to afford 24.2 mg  
(74%) of the title compound as a white solid.

20

<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, δ) 7.205 (d, 1H, J = 2.2 Hz), 6.925  
(dd, 1H, J = 8.8 Hz, 2.2 Hz), 6.72 (d, 1H, J = 8.2 Hz), 6.19  
(s, 1H), 4.10 (s, 2H), 3.25 (heptet, 1H, J = 6.6 Hz),  
1.185, 1.165 (2d, 6H, J = 7.2, 6.6 Hz)  
25 MS-ESI<sup>-</sup> [M-H]<sup>-</sup> = 410, 412, 414 (100:64:10)

#### Example 57

30 **[3,5-Dichloro-6-fluoro-4-(4-hydroxy-3-isopropyl-benzoyl)-  
pyridin-2-ylamino]-acetic acid**



5

To a solution of crude {3,5,dichloro-4-[cyano-(4-hydroxy-3-isopropyl-phenyl)-methyl]-6-fluoro-pyridin-2-ylamino}-acetic acid (24 mg, 0.058 mmol) in DMSO (2 mL) was added K<sub>2</sub>CO<sub>3</sub> (28 mg, 0.202 mmol) in H<sub>2</sub>O (2 mL). The mixture was left to stir overnight at ambient room temperature in an open flask. The mixture was acidified with 1N HCl and the product was partitioned between EtOAc (50 mL) and H<sub>2</sub>O (25 mL). The organic extract was washed with brine (25 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered and concentrated in vacuo.

15 The crude product was purified by preparative HPLC (from 50% B to 100% B for 10 min, Solvent A = 90% H<sub>2</sub>O-10% MeOH-0.1% TFA Solvent B = 10% MeOH-90% H<sub>2</sub>O-0.1% TFA, at 20 mL/min using column YMC ODS S5 20 x 100 mm) to afford 7.95 mg (34% for 2 steps) of the title compound.

20

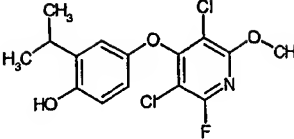
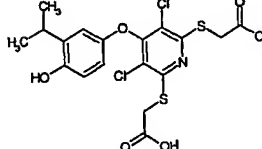
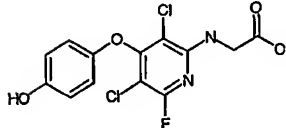
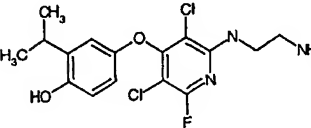
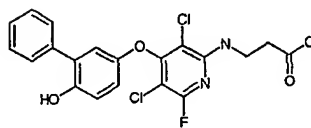
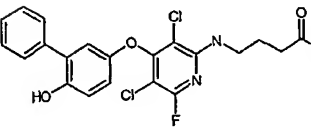
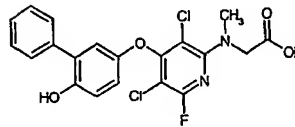
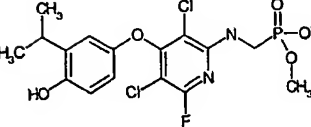
<sup>1</sup>H NMR (400 MHz, CD<sub>3</sub>OD, δ) 7.77 (d, 1H, J = 1.1 Hz), 7.435 (dd, 1H, J = 8.8 Hz, 2.2 Hz), 6.82 (d, 1H, J = 8.3 Hz), 4.14 (s, 1H), 4.12 (s, 1H), 3.30-3.27 (m, 1H), 1.225 (d, 6H, J = 6.6 Hz)

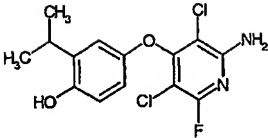
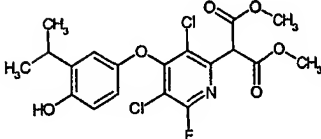
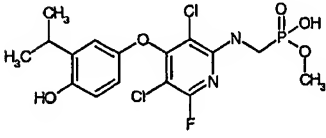
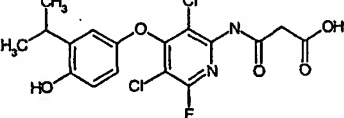
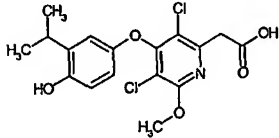
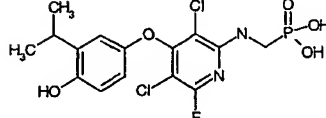
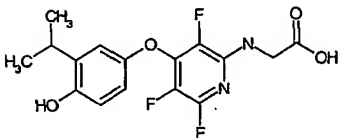
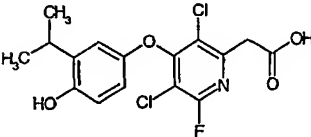
25 MS-ESI<sup>-</sup> [M-H]<sup>-</sup> = 399, 401, 403 (100:64:10)

The following examples were prepared using the procedures or a variation thereof, as described in the aforementioned examples and schemes.

30

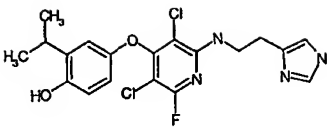
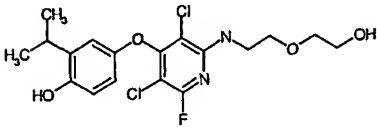
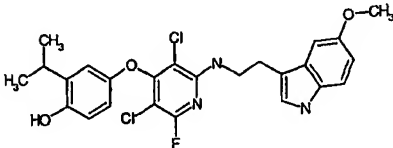
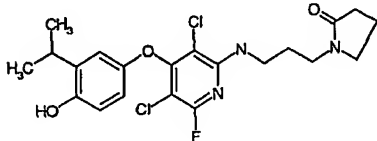
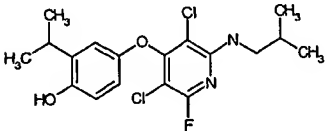
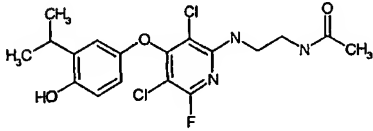
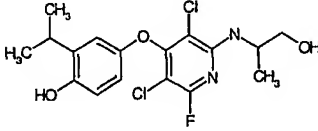
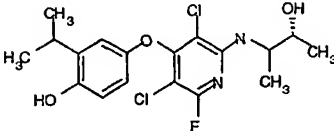
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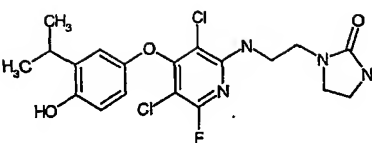
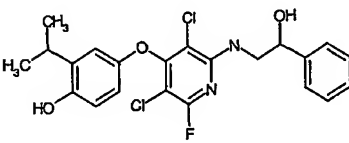
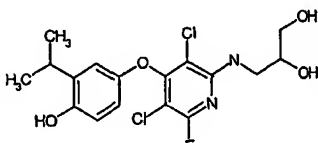
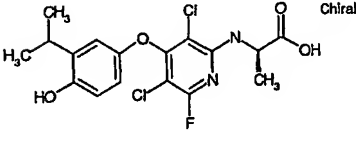
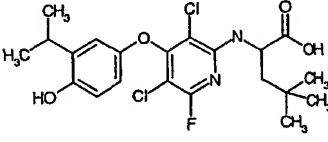
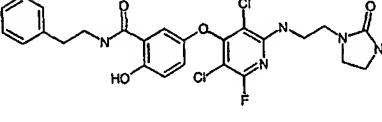
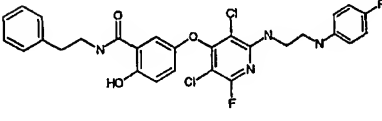
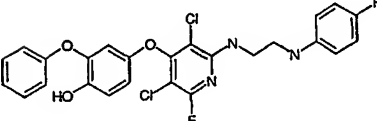
Example #	Structure	molecular weight	[M+H] <sup>+</sup>	[M-H] <sup>-</sup>
58		346.19		343.88
59		478.37		475.74
60		347.13		344.85
61		374.25	374	372
62		437.26		435
63		451.29		449
64		437.26		435
65		453.24	455	

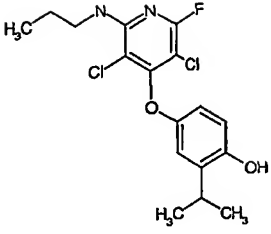
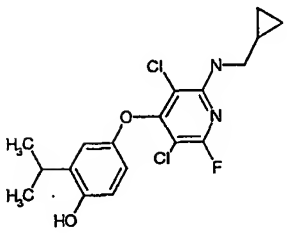
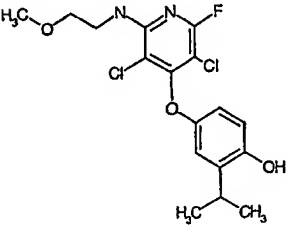
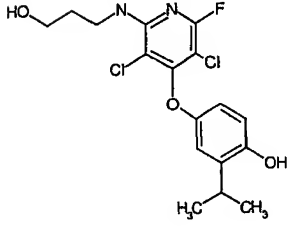
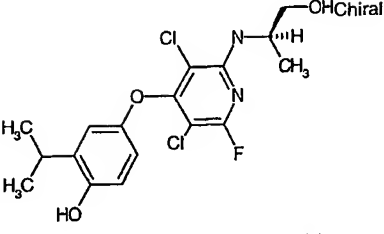
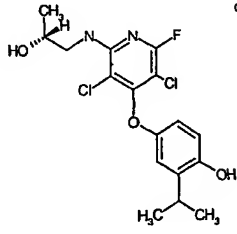
66		331.18	328.9
67		446.26	444
68		439.21	436.9
69		417.22	415
70		386.23	385.9
71		425.18	422.8
72		356.3	355
73		374.2	372.1


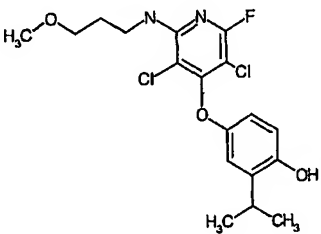
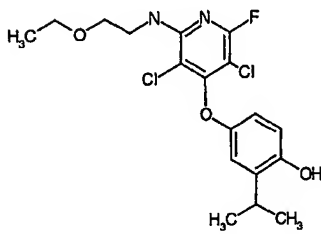
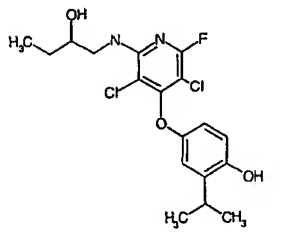
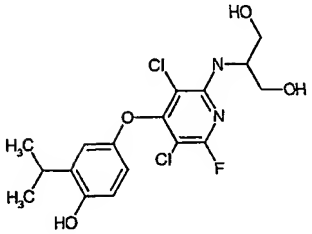
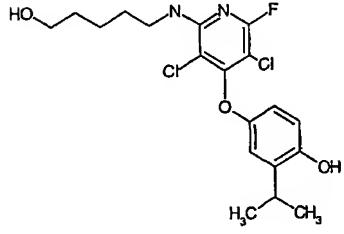


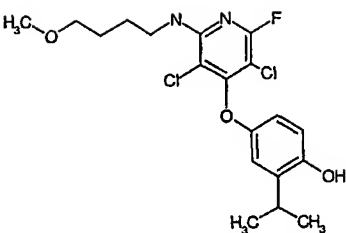
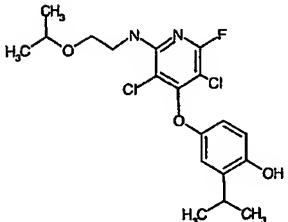
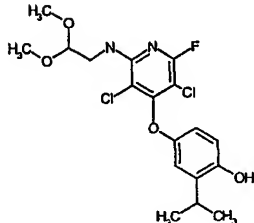
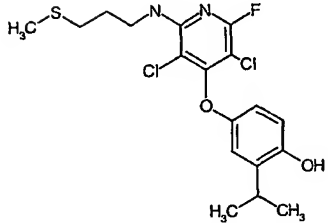
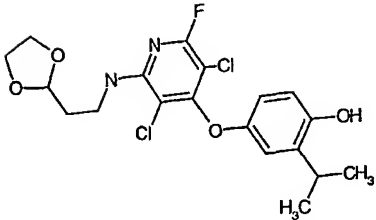
5

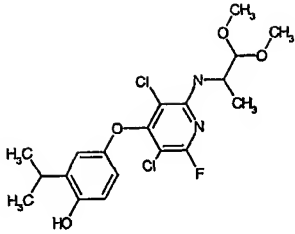
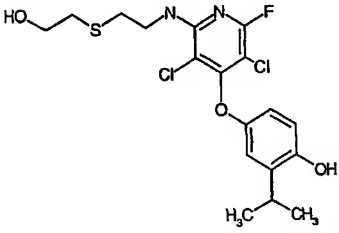
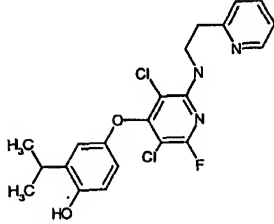
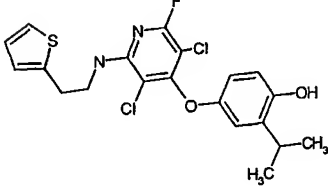
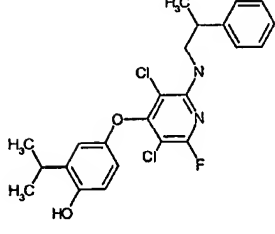
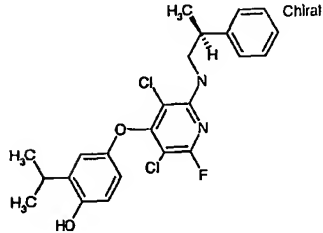
74		425.29	426	424
75		419.28	419	417
76		504.39	505	502
77		456.35	456	
78		387.28		386
79		416.28	416	415
80		389.26	389	387
81		403.28	403	401

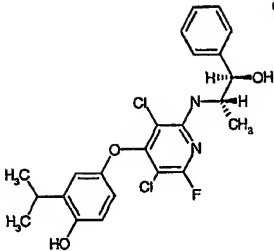
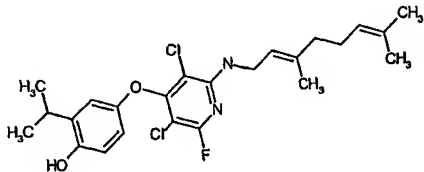
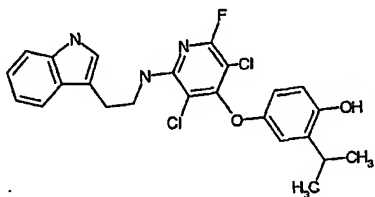
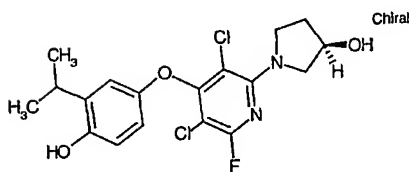
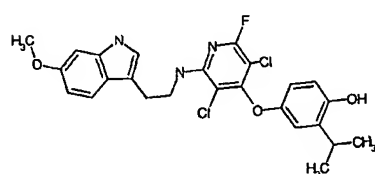
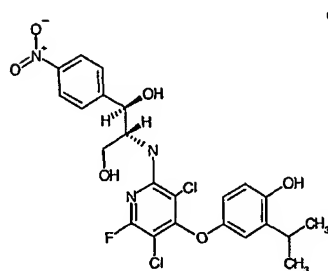
82		440.31	441	
83		451.33	451	449
84		404.27	405	403
85		403.24	401	
86		459.35		457
87		546.39	548	
88		573.43		571
89		518.35		516

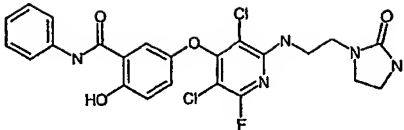
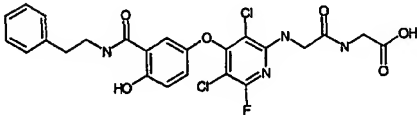
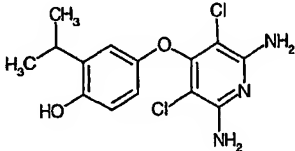
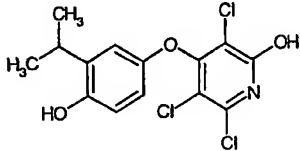
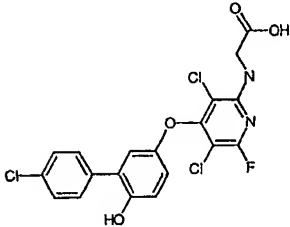
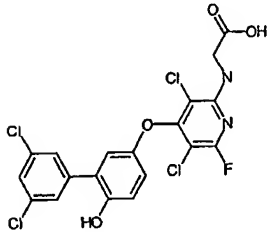
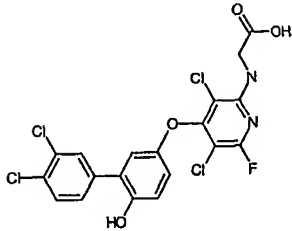
90		373.3	373	
91		385.3	385	383
92		389.3		387
93		389.3		387
94		389.3	389	387
95		389.3	389	387

96		403.3	403	401
97		403.3	403	401
98		403.3	403	401
99		403.3	403	401
100		405.3	405	403
101		417.3	417	415

102		417.3	417	415
103		417.3	417	415
104		419.3		417
105		419.3	419	417
106		431.3	431	

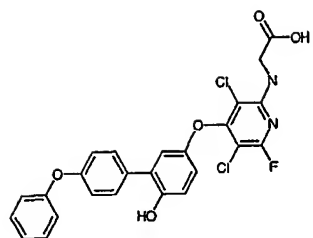
107		433.3		431
108		435.3	435	433
109		436.3	436	434
110		441.4	441	
111		449.4	449	447
112		449.4	450	

113	 <chem>CC(C)c1cc(O)ccc1Oc2nc(Cl)c(Cl)c(F)n2C[C@H](O)[C@H](C)c3ccccc3</chem>	465.4	465	
114	 <chem>CC(C)c1cc(O)ccc1Oc2nc(Cl)c(Cl)c(F)n2C/C=C/C(C)CC(C)=C</chem>	467.4	465	
115	 <chem>CC(C)c1cc(O)ccc1Oc2nc(Cl)c(Cl)c(F)n2CNCCc3c4ccccc4n3</chem>	474.4	474	472
116	 <chem>CC(C)c1cc(O)ccc1Oc2nc(Cl)c(Cl)c(F)n2N[C@H]1CC[C@H](O)C1</chem>	401.3	401	399
117	 <chem>COc1ccc2c(c1)c3ccccc3n2CNCCc4c5ccccc5n4</chem>	504.4	504	502
118	 <chem>CC(C)c1cc(O)ccc1Oc2nc(Cl)c(Cl)c(F)n2C[C@H](O)[C@H](O)[C@H](O)[C@H](O)c3ccc([N+](=O)[O-])cc3</chem>	526.3	526	524

119		520.35	518
120		551.36	549
121		328.2	328.05
122		348.62	345.9
123		457.7	455
124		492.1	491
125		492.1	491



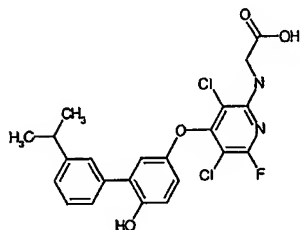
126



515.3

515

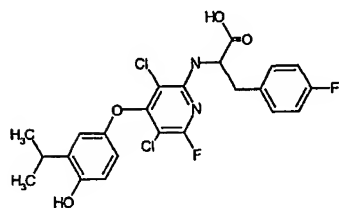
127



465.3

465

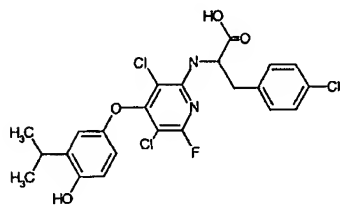
128



497.3

497

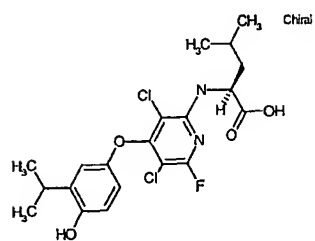
129



513.8

514

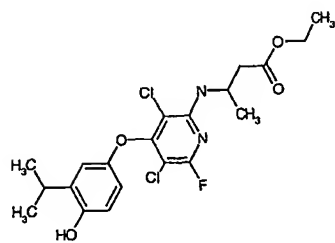
130



445.3

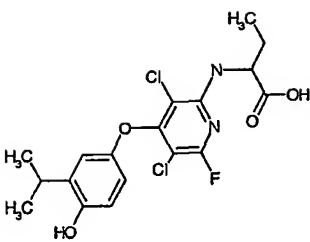
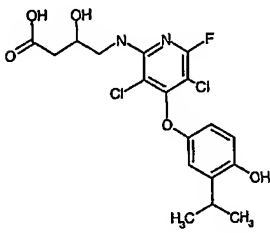
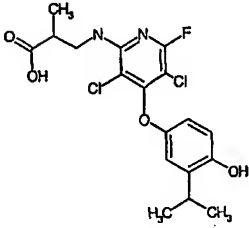
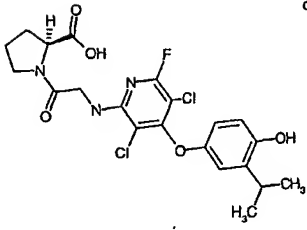
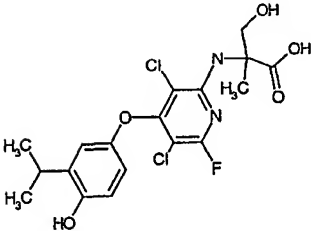
445

131

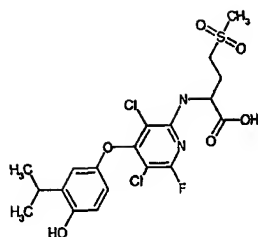


445.3

455

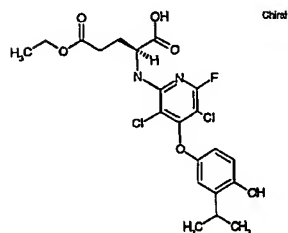
132		417.3	417
133		433.3	433
134			417
135	 Chiral		485.91
136			432.86

137



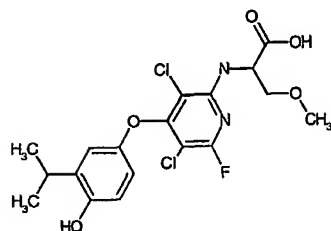
494.85

138



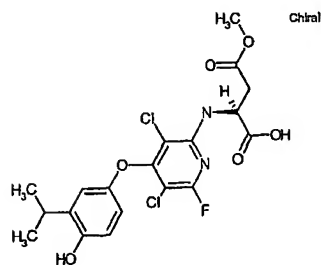
488.88

139



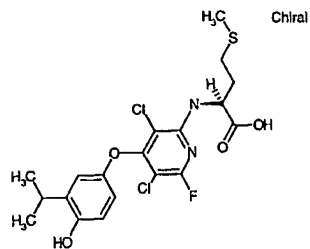
432.86

140

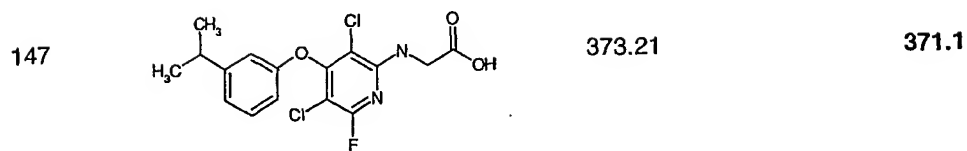
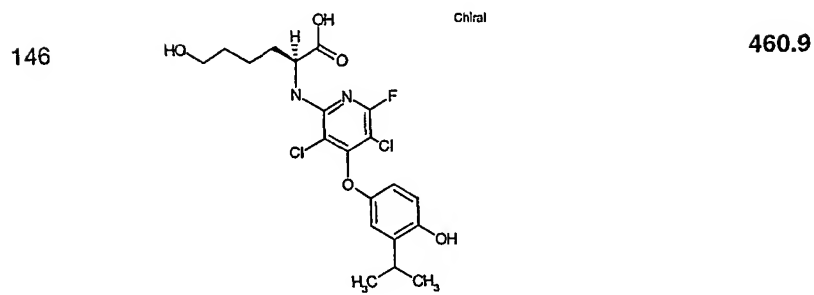
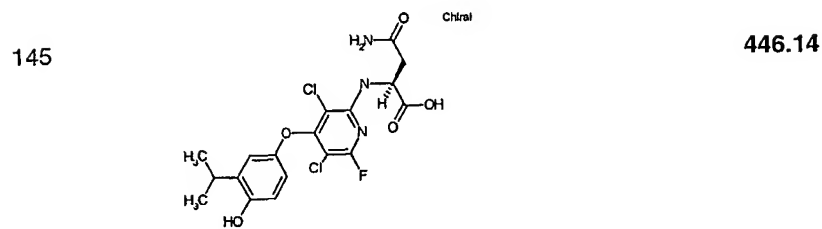
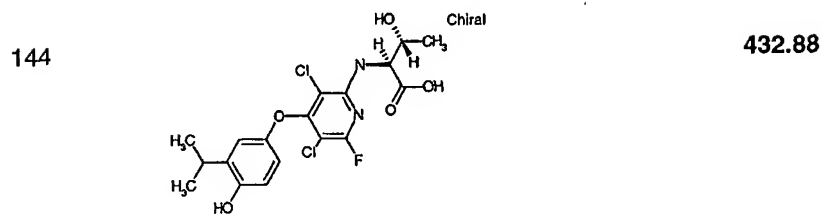
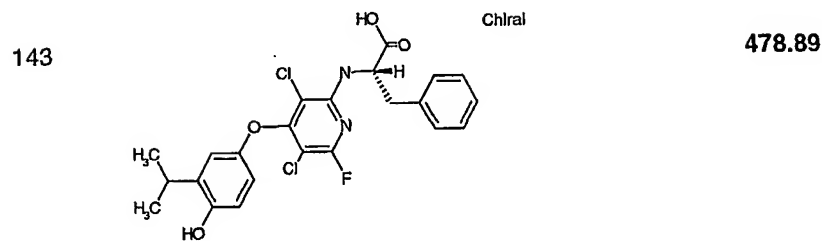
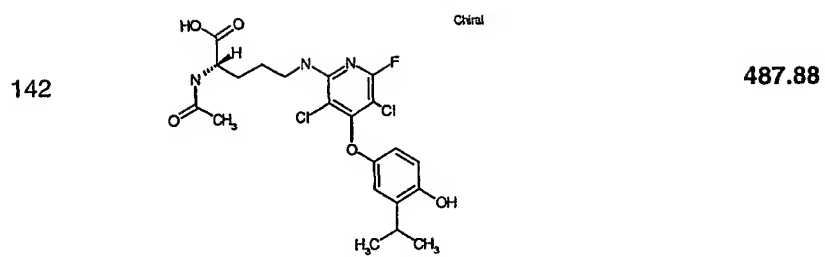


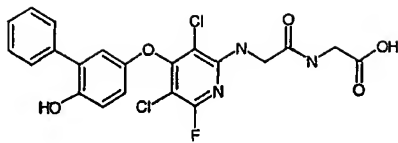
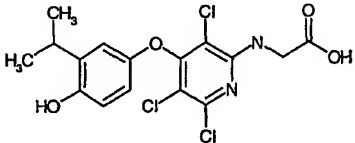
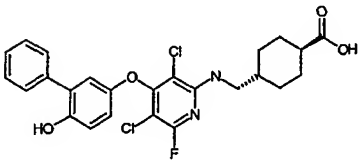
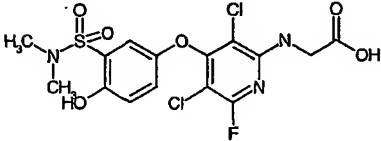
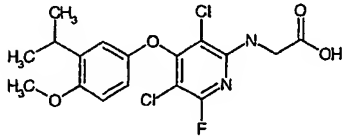
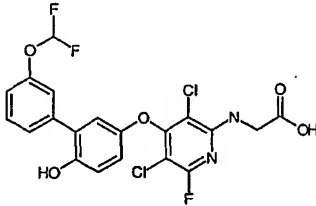
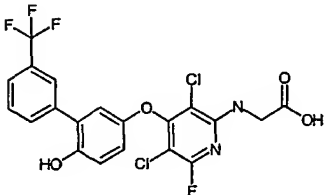
461

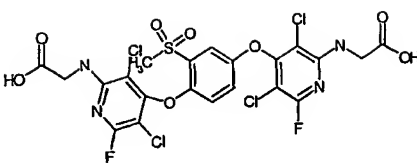
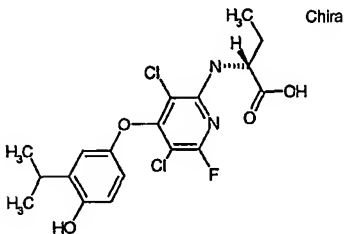
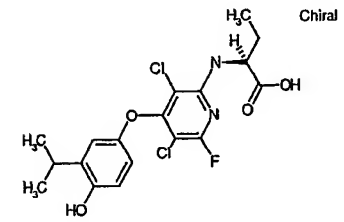
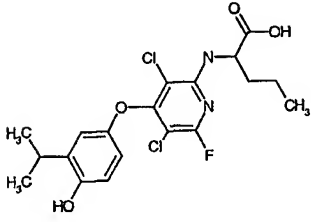
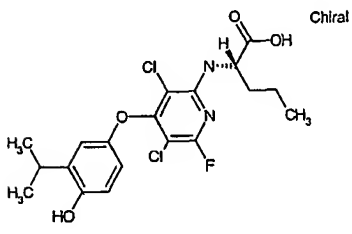
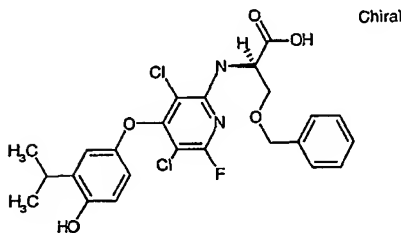
141



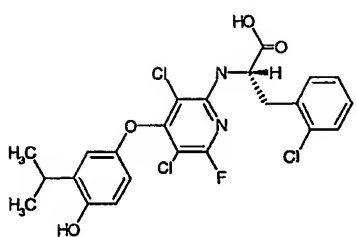
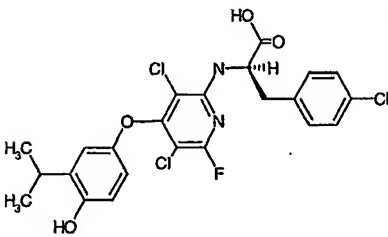
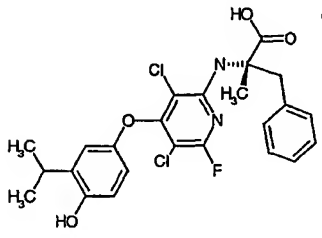
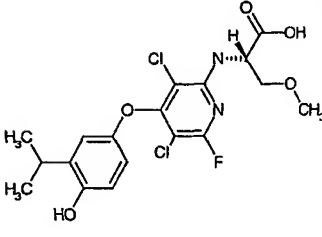
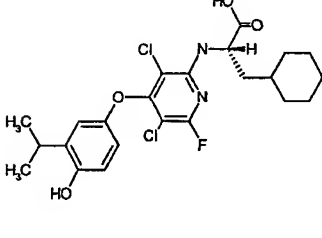
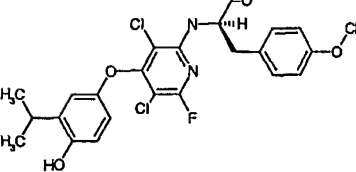
462.87



148		480.28	478
149		405.67	403.1
150		505.38	503
151		454.26	452
152		403.24	401.3
153		489.24	487
154		491.23	489

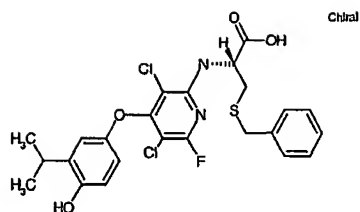
155		662.24	661
156		417.3	417.16
157		417.3	417.15
158		431.3	431.16
159		431.3	431.16
160		509.4	509.19

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166		513.8	514
167		513.8	514
168		493.4	493.16
169		433.3	433.15
170		485.4	485.17
171		509.4	509.17



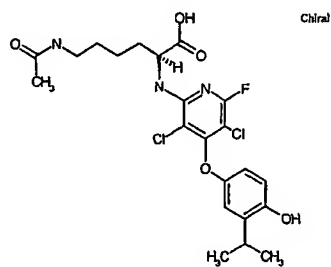
172



525.4

525.14

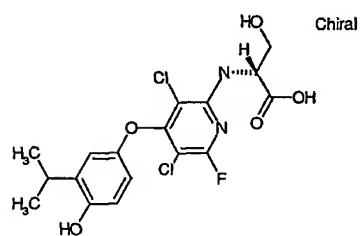
173



502.4

502.19

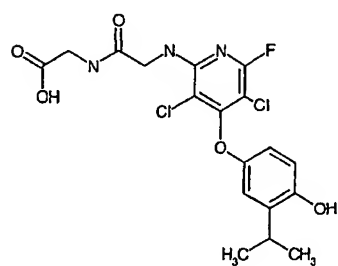
174



419.2

419.15

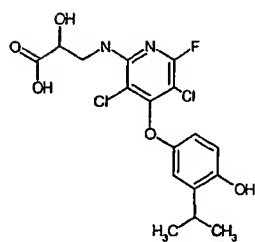
175



446.3

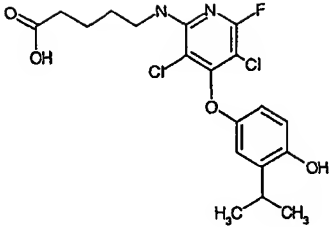
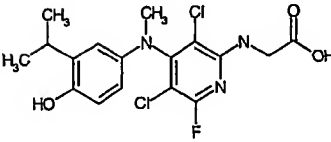
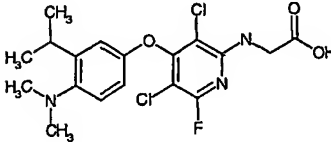
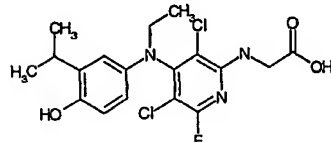
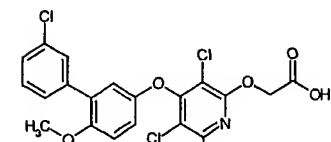
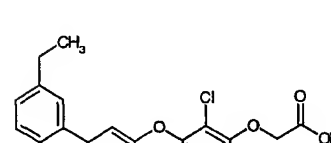
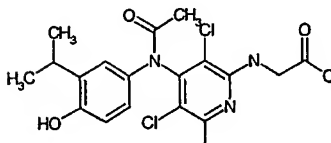
446.12

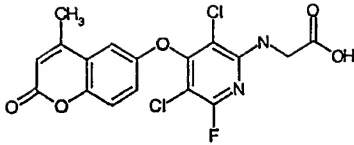
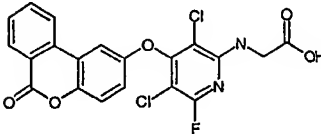
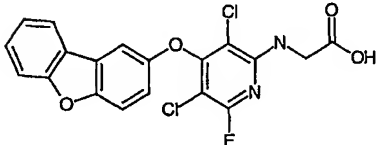
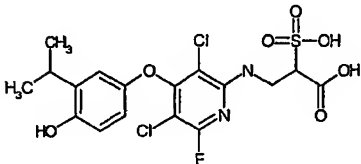
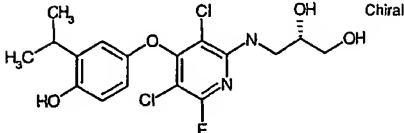
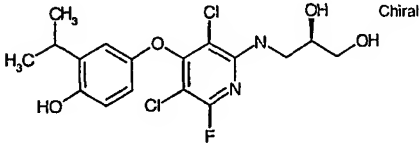
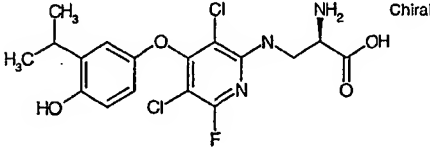
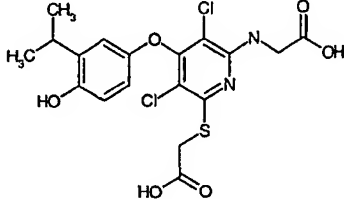
176

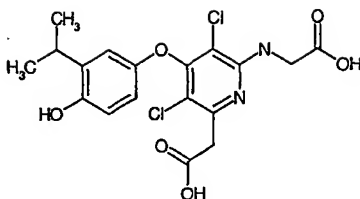
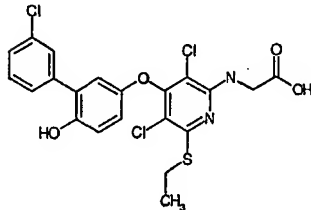
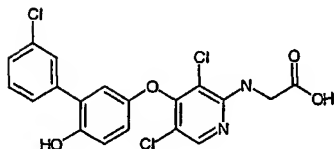
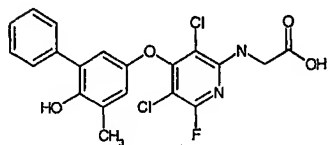
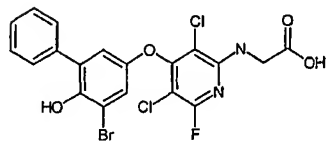
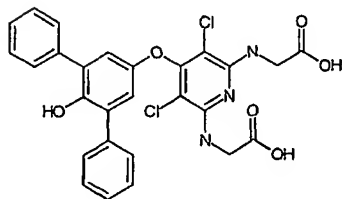
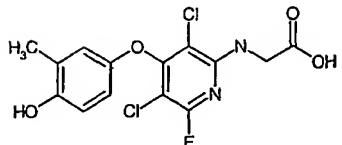


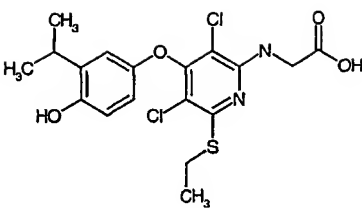
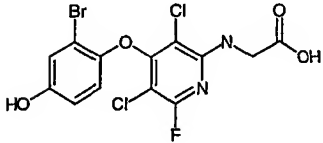
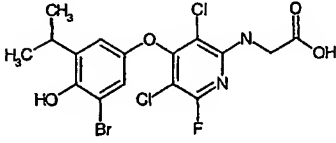
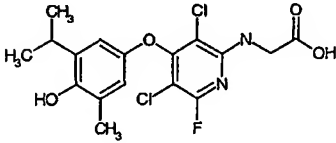
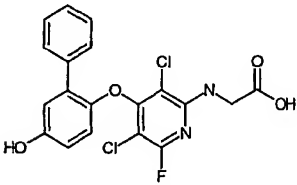
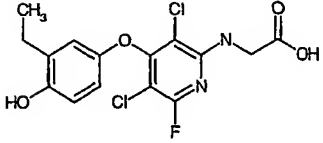
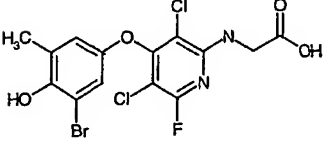
419.2

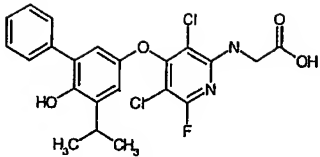
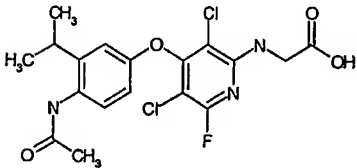
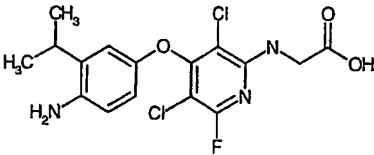
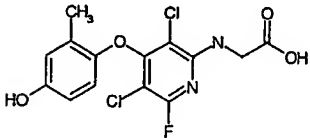
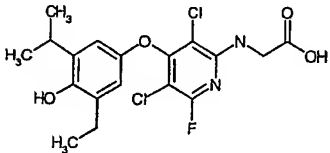
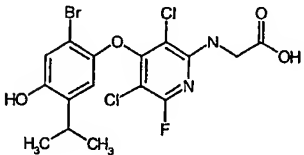
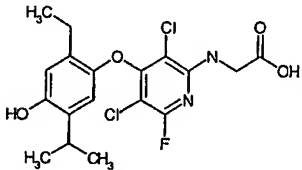
419.13

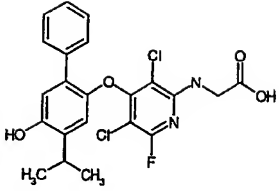
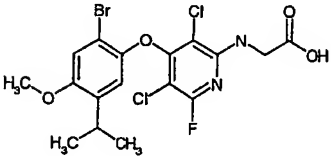
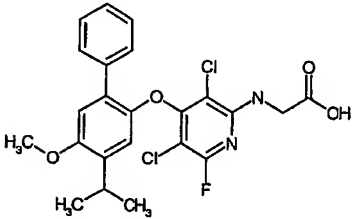
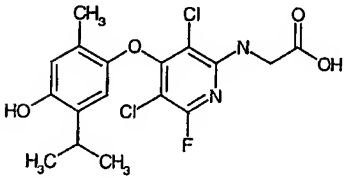
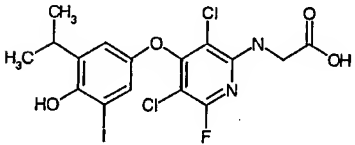
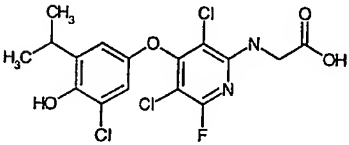
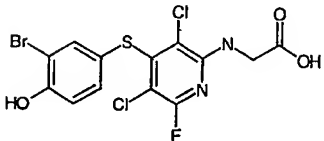
177		431.3	431.3	
178		402.26	402.1	400.1
179		416.28	416.21	
180		416.28		414.23
181		472.69		471.6
182		466.3		463.7
183		430.27	430.38	428.34

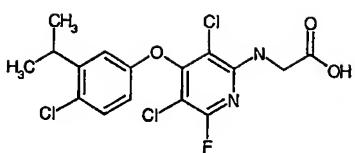
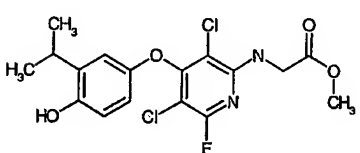
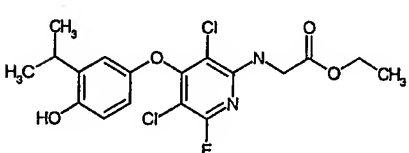
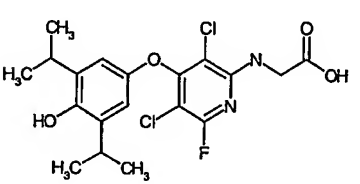
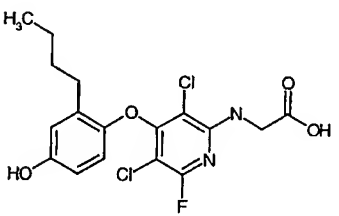
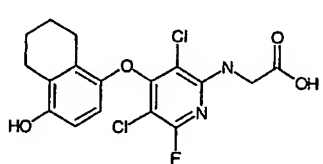
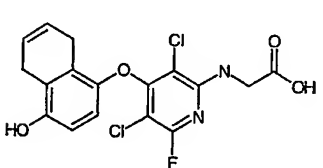
184		413.19	410.6	
185		449.23	446.6	
186		421.21	418.7	
187		483.3	481.28	
188		405.26	403	
189		405.26	403	
190		418.26	418.1	415.9
191		461.32	459	

192		429.26	429	
193		499.8	499.1	
194		439.69	439	
195		437.26	437	435
196		502.13	502	
197		554.39	554	
198		361.16	359	

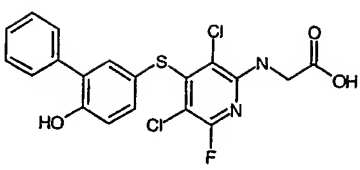
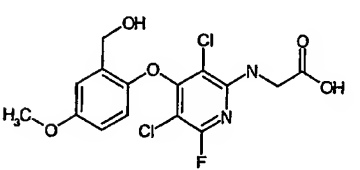
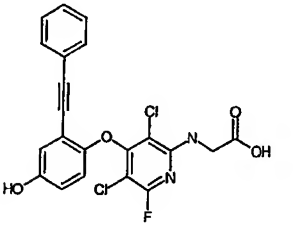
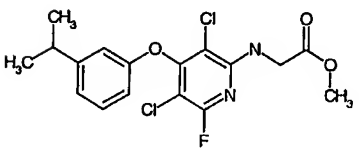
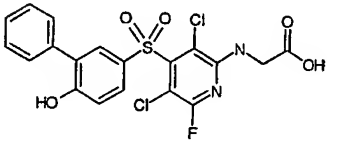
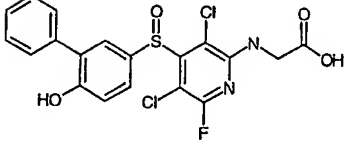
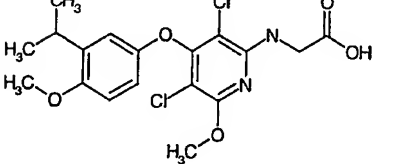
199		431.34	428.8
200		426.03	424.9
201		468.11	466
202		403.24	401
203		423.23	421
204		375.19	373
205		440.06	438

206		465.31		463
207		430.27	430.18	428.1
208		388.23	388.11	386
209		361.16		358.9
210		417.27		415
211		468.11		466
212		417.27		415

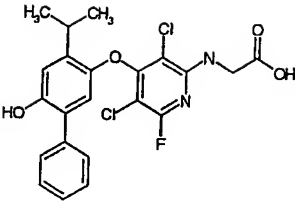
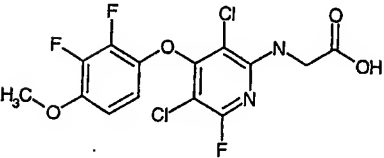
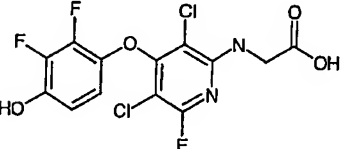
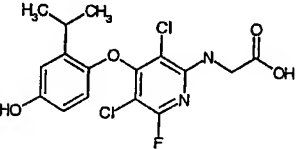
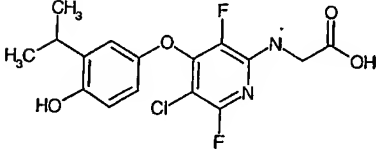
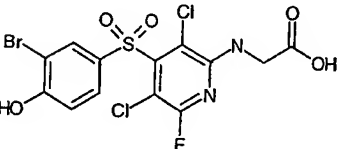
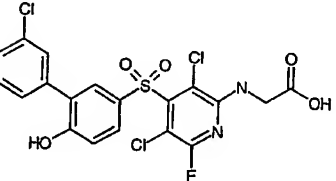
213		465.31	463
214		482.14	481
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216		403.24	401
217		515.11	513
218		423.66	421
219		442.09	438.88

220		407.66	405.02
221		403.24	401
222		417.27	414.9
223		431.29	429
224		403.24	401
225		401.22	399
226		399.21	396.9



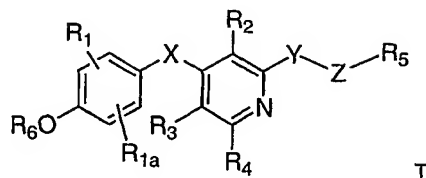
227		439.3	437.11
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229		447.25	445
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231		471.29	468.98
232		455.29	452.98
233		415.28	414

234		446.27		444
235		433.33	433.13	431.1
236				463.01
237		437.26		435
238		462.01		460
239		459.21		457
240		468.11		466

241		465.31	463
242		397.14	395
243		383.11	381
244		389.21	386.9
245		372.76	370.8
246		474.09	472.7
247		505.74	504.8

5 What is claimed is:

1. A compound of the formula



10

wherein

X is selected from the group consisting of oxygen, sulfur, sulfoxide, sulfonyl,  $-CR_8R_8'$  and  $-NR_8$ ;

Y is selected from the group consisting of  $-NR_8$ ,  
 15 oxygen,  $-CH_2-$  and sulfur;

Z is a bond or substituted or unsubstituted  $C_{1-4}$  alkyl;

$R_1$  is selected from the group consisting of halogen, trifluoromethyl, substituted or unsubstituted  $C_{1-6}$  alkyl, substituted or unsubstituted aryl, substituted or  
 20 unsubstituted heteroaryl, aryloxy, substituted amide, sulfone, sulfonamide and  $C_{3-7}$  cycloalkyl, wherein said aryl, heteroaryl or cycloalkyl ring(s) are attached or fused to the aromatic ring;

$R_{1a}$  is selected from the group consisting of hydrogen,  
 25 halogen, substituted or unsubstituted  $C_{1-6}$  alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

$R_2$  and  $R_3$  are each independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted  $C_{1-4}$  alkyl and unsubstituted or substituted  $C_{3-5}$   
 30 cycloalkyl, wherein at least one of  $R_2$  and  $R_3$  being other than hydrogen;

$R_4$  is selected from the group consisting of hydrogen, halogen, amino, O-R, and S-R;

5            $R_5$  is selected from the group consisting of hydroxyl, carboxylic acid, sulfonic acid and phosphonic acid;

$R_6$  is selected from the group consisting of hydrogen, alkyl, alkanoyl and aroyl;

$R_7$  is hydrogen or  $C_{1-4}$  alkyl;

10            $R_8$  for each occurrence is independently selected from the group consisting of hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, aryl  
15 or substituted aryl, arylalkyl or substituted arylalkyl, alkoxy and hydroxyl; and

$R_8'$  is selected from the group consisting of hydrogen, a bond, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl  
20 or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, aryl or substituted aryl, arylalkyl or substituted arylalkyl, alkoxy and hydroxyl, or  $R_8$  and  $R_8'$  together form a carbonyl,

          including all prodrug, stereoisomers and  
25 pharmaceutically acceptable salts thereof.

2. The compound as defined in claim 1 wherein

          X is selected from the group consisting of oxygen, sulfur, sulfoxide, sulfonyl,  $-CH_2-$  and  $-NH-$ ;

30           Y is  $-NH-$  or oxygen;

$R_1$  is selected from the group consisting of halogen, substituted or unsubstituted  $C_{1-6}$  alkyl, substituted aryl, aryloxy, substituted amide, sulfone, sulfonamide and  $C_{3-7}$  cycloalkyl, wherein  $R_1$  is attached ortho to the  $R_6O$  group;

35            $R_2$  and  $R_3$  are each independently selected from the group consisting of iodo, bromo, chloro and fluoro;

$R_4$  is selected from the group consisting of hydrogen, fluoro, chloro, amino,  $-OCH_3$  and hydroxyl;

5           R<sub>5</sub> is carboxylic acid; and  
             R<sub>6</sub> is hydrogen.

            3. The compound as defined in claim 1 wherein  
             X is selected from the group consisting of carbonyl,  
 10    CHR<sub>8</sub> and NR<sub>8</sub>;

            Y is oxygen or -NH-;

            R<sub>1</sub> is selected from the group consisting of halogen,  
             substituted or unsubstituted C<sub>1-6</sub> alkyl, substituted aryl,  
             substituted amide, sulfone, sulfonamide and C<sub>3-7</sub> cycloalkyl;

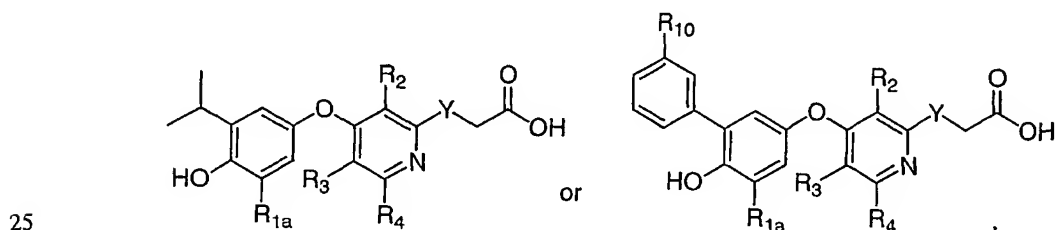
15           R<sub>2</sub> and R<sub>3</sub> each independently are selected from the  
             group consisting of bromo, chloro and methyl;

            R<sub>4</sub> is selected from the group consisting of hydrogen,  
             fluoro, chloro, hydroxyl, amino and methoxy;

            R<sub>5</sub> is carboxylic acid; and

20           R<sub>6</sub> is hydrogen.

            4. The compound as defined in claim 1 having the  
             structure



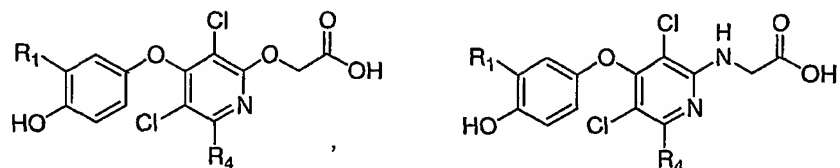
5. The compound as defined in claim 4 wherein  
             Y is oxygen or -NH-;  
             R<sub>2</sub> and R<sub>3</sub> are halogen;  
 30           R<sub>4</sub> is selected from the group consisting of hydrogen,  
             halogen, amino, -OCH<sub>3</sub> and hydroxyl; and

            R<sub>10</sub> is selected from the group consisting of hydrogen,  
             halogen and substituted and unsubstituted C<sub>1-4</sub> alkyl.

            R<sub>1a</sub> is selected from hydrogen, methyl and ethyl.

5

6. The compound as defined in claim 1 having the structure

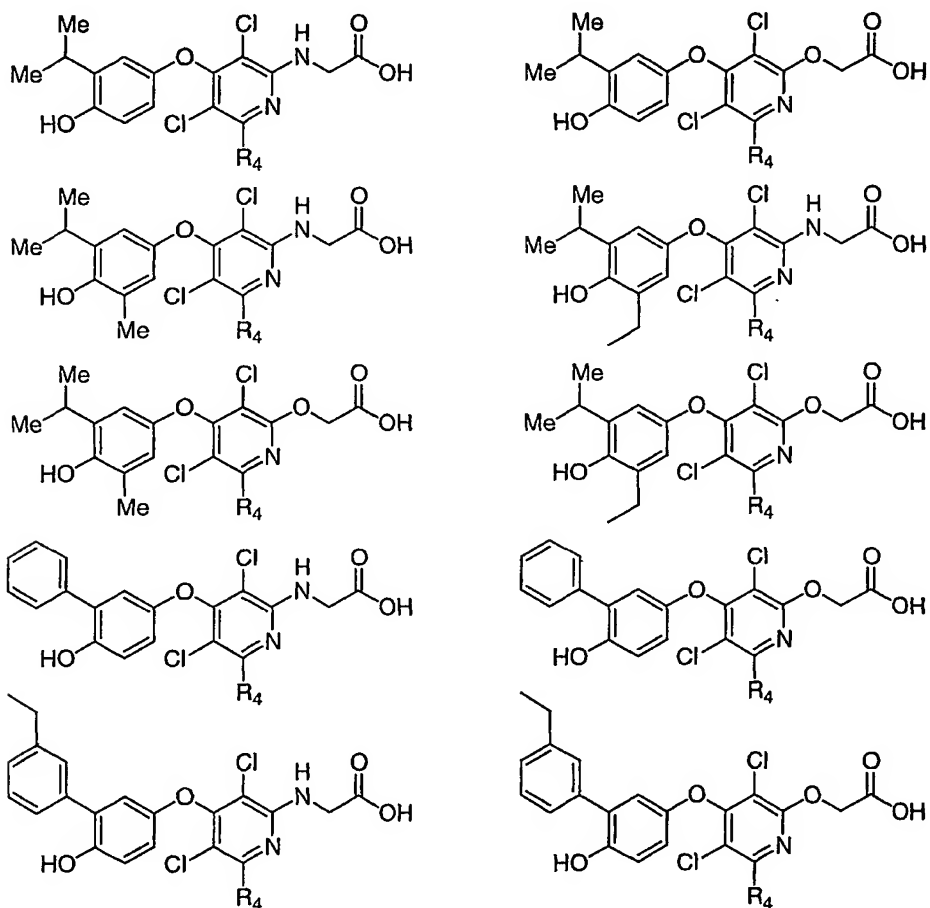


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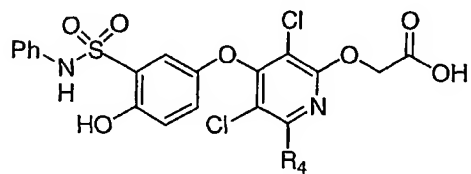
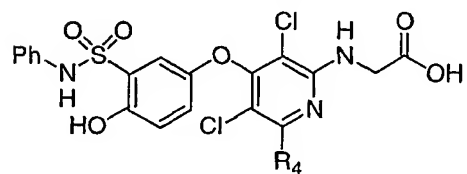
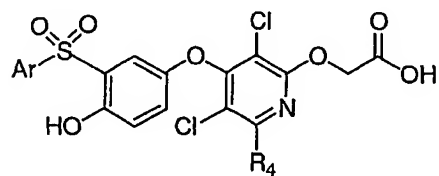
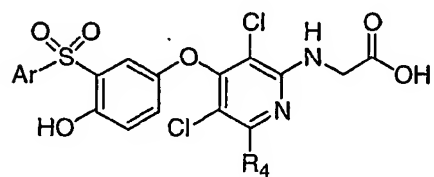
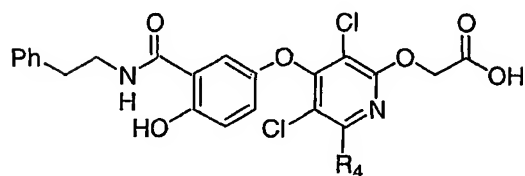
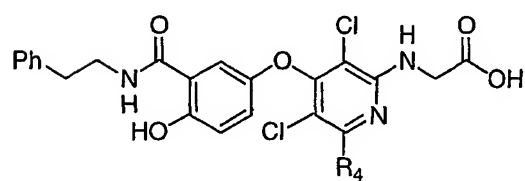
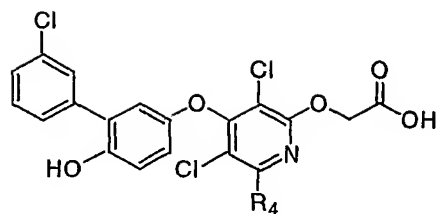
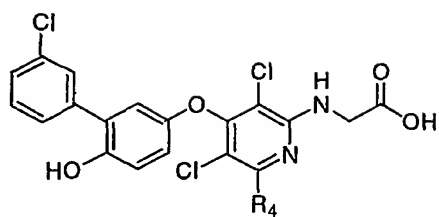
wherein  $R_1$  is substituted or unsubstituted aryl.

7. The compound as defined in claim 1 having the structure

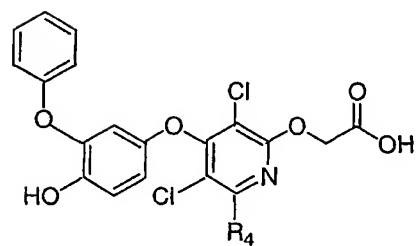
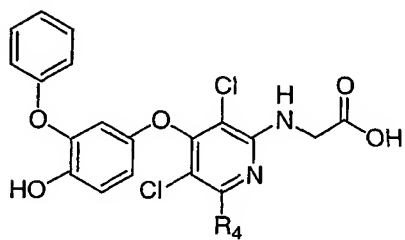
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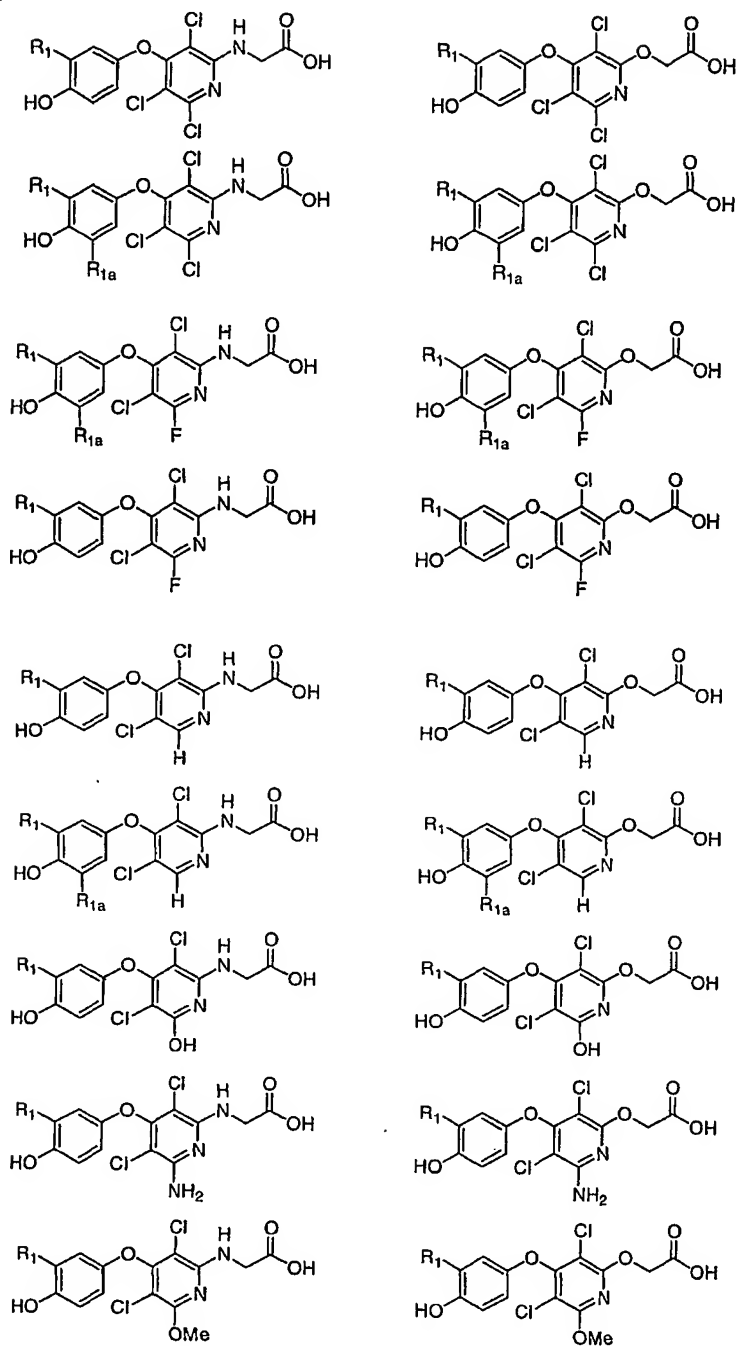
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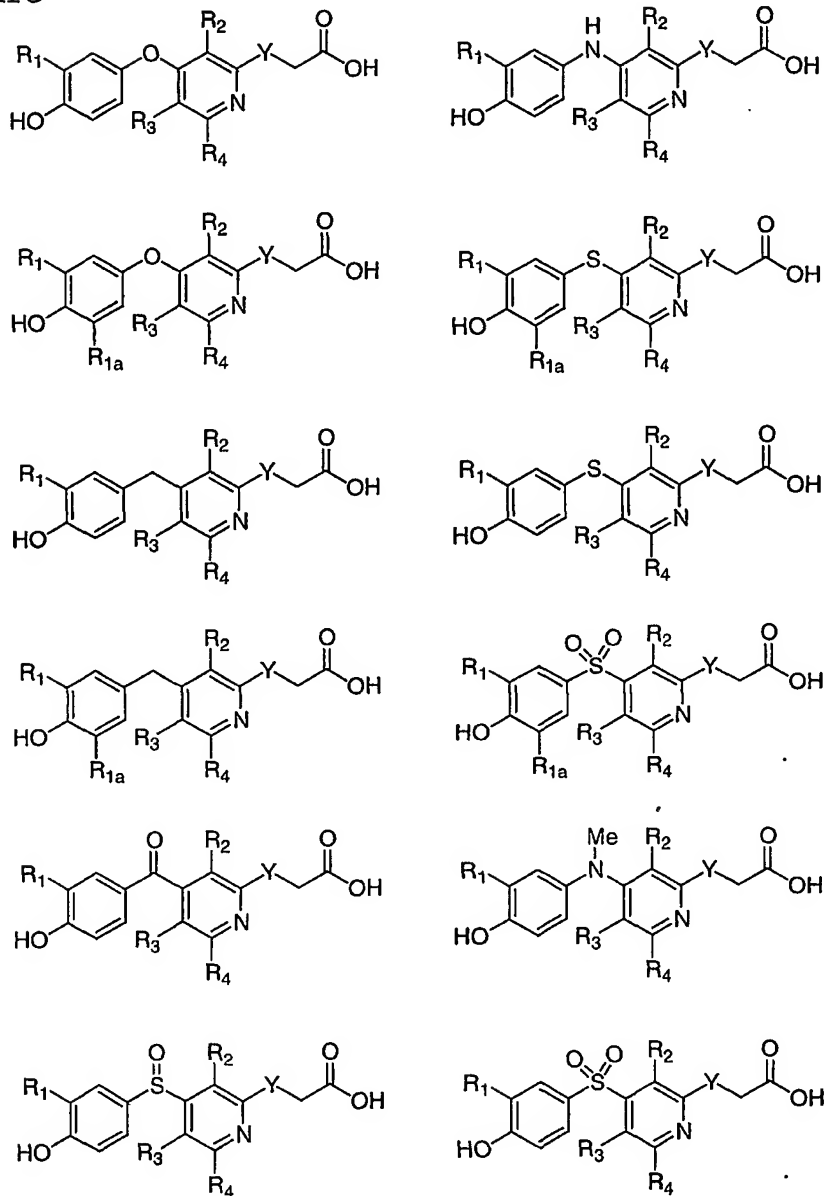
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8. The compound as defined in claim 1 having the structure



10

- 5            9. The compound as defined in claim 1 having the structure



- 10            10. A pharmaceutical composition comprising a compound as defined in claim 1 and a pharmaceutically acceptable carrier therefor.

5           11. The pharmaceutical composition of claim 10  
further comprising at least one additional therapeutic agent  
selected from the group consisting of other compounds of  
formula I, anti-diabetic agents, anti-osteoporosis agents,  
anti-obesity agents, growth promoting agents, anti-  
10 inflammatory agents, anti-anxiety agents, anti-depressants,  
anti-hypertensive agents, cardiac glycosides,  
cholesterol/lipid lowering agents, appetite suppressants,  
bone resorption inhibitors, thyroid mimetics, anabolic  
agents, anti-tumor agents and retinoids.

15

          12. The pharmaceutical composition of claim 11  
wherein said additional therapeutic agent is an antidiabetic  
agent selected from the group consisting of a biguanide, a  
glucosidase inhibitor, a meglitinide, a sulfonylurea, a  
20 thiazolidinedione, a PPAR-alpha agonist, a PPAR-gamma  
agonist, a PPAR alpha/gamma dual agonist, an SGLT2  
inhibitor, a glycogen phosphorylase inhibitor, an aP2  
inhibitor, a glucagon-like peptide-1 (GLP-1), a dipeptidyl  
peptidase IV inhibitor and insulin.

25

          13. The pharmaceutical composition of claim 11  
wherein said additional therapeutic agent is an  
antidiabetic agent selected from the group consisting of  
metformin, glyburide, glimepiride, glipyrider, glipizide,  
30 chlorpropamide, gliclazide, acarbose, miglitol,  
troglitazone, pioglitazone, englitazone, darglitazone,  
rosiglitazone and insulin

          14. The pharmaceutical composition of claim 11  
35 wherein said additional therapeutic agent is an anti-obesity  
agent is selected from the group consisting of an aP2  
inhibitor, a PPAR gamma antagonist, a PPAR delta agonist, a

5    beta 3 adrenergic agonist, a lipase inhibitor, a serotonin reuptake inhibitor and an anorectic agent.

15            15. The pharmaceutical composition of claim 11 wherein said additional therapeutic agent is a hypolipidemic agent selected from the group consisting of a  
10    thiazolidinedione, an MTP inhibitor, a squalene synthetase inhibitor, an HMG CoA reductase inhibitor, a fibric acid derivative, an ACAT inhibitor, a cholesterol absorption inhibitor, an ileal Na<sup>+</sup>/bile cotransporter inhibitor, a bile  
15    acid sequestrant and a nicotinic acid or a derivative thereof.

20            16. A method for preventing, inhibiting or treating a disease associated with metabolism dysfunction, or which is dependent on the expression of a T<sub>1</sub> regulated gene, which  
20    comprises administering to a mammalian patient in need of treatment a therapeutically effective amount of a compound as defined in claim 1.

25            17. A method for treating or delaying the progression or onset of obesity, hypercholesterolemia, atherosclerosis, depression, osteoporosis, hypothyroidism, subclinical hyperthyroidism, non-toxic goiter, reduced bone  
30    mass, density or growth, eating disorders, reduced cognitive function, thyroid cancer, glaucoma, cardiac arrhythmia, congestive heart failure or a skin disorder or disease, which comprises administering to mammalian patient  
35    in need of treatment a therapeutically effective amount of a compound as defined in claim 1.

18. The method according to claim 17 wherein the skin disorder or disease is dermal atrophy, keloids, stria, cellulite, roughened skin, actinic skin damage, lichen

5 planus, ichthyosis, acne, psoriasis, Dernier's disease,  
eczema, atopic dermatitis, chloracne, pityriasis or skin  
scarring.

19. The method according to claim 17 further  
10 comprising administering, concurrently or sequentially, a  
therapeutically effective amount of at least one additional  
therapeutic agent selected from the group consisting of  
other compounds of formula I, anti-diabetic agents, anti-  
osteoporosis agents, anti-obesity agents, growth promoting  
15 agents, anti-inflammatory agents, anti-anxiety agents,  
anti-depressants, anti-hypertensive agents, cardiac  
glycosides, cholesterol/lipid lowering agents, appetite  
suppressants, bone resorption inhibitors, thyroid mimetics,  
anabolic agents, anti-tumor agents and retinoids.

20

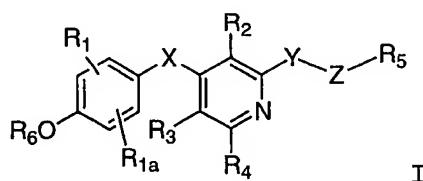
20. A method of treating or delaying the progression  
or onset of a skin disorder or disease which comprises  
administering to a mammalian patient a therapeutically  
effective amount of a compound as defined in claim 1 in  
25 combination with a retinoid or a vitamin D analog.

21. A method for treating or delaying the progression  
or onset of obesity which comprises administering to  
mammalian patient in need of treatment a therapeutically  
30 effective amount of a compound as defined in Claim 1.

22. A method according to claim 21 further comprising  
administering, concurrently or sequentially, a  
therapeutically effective amount of at least one additional  
35 therapeutic agent selected from the group consisting of an  
anti-obesity agent and an appetite suppressant.

5           23. A method according to claim 22 wherein said anti-obesity agent is selected from the group consisting of aP2 inhibitors, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, lipase inhibitors, serotonin (and dopamine) reuptake inhibitors, other thyroid receptor  
10   beta agents and anorectic agents.

24. A compound of the formula



15

wherein

X is selected from the group consisting of oxygen, sulfur, sulfoxide, sulfonyl,  $-CR_8R_8'$  and  $-NR_8$ ;

Y is selected from the group consisting of  $-NR_8$ ,  
20   oxygen,  $-CH_2-$  and sulfur;

Z is a bond or substituted or unsubstituted  $C_{1-4}$  alkyl;

$R_1$  is selected from the group consisting of halogen, trifluoromethyl, substituted or unsubstituted  $C_{1-6}$  alkyl, substituted or unsubstituted aryl, substituted or  
25   unsubstituted heteroaryl, aryloxy, substituted amide, sulfone, sulfonamide and  $C_{3-7}$  cycloalkyl;

$R_{1a}$  is selected from the group consisting of hydrogen, halogen, substituted or unsubstituted  $C_{1-6}$  alkyl, substituted or unsubstituted aryl and substituted or unsubstituted  
30   heteroaryl;

$R_2$  and  $R_3$  are each independently selected from the group consisting of hydrogen, halogen, unsubstituted or substituted  $C_{1-4}$  alkyl and unsubstituted or substituted  $C_{3-5}$  cycloalkyl, wherein at least one of  $R_2$  and  $R_3$  being other  
35   than hydrogen;

- 5            $R_4$  is selected from the group consisting of hydrogen, halogen, amino, O- $R_7$ , S- $R_7$ , and unsubstituted or substituted  $C_{1-4}$  alkyl;
- $R_5$  is selected from the group consisting of hydroxyl, carboxylic acid, sulfonic acid and phosphonic acid;
- 10            $R_6$  is selected from the group consisting of hydrogen, alkyl, alkanoyl and aroyl;
- $R_7$  is hydrogen or  $C_{1-4}$  alkyl;
- $R_8$  for each occurrence is independently selected from the group consisting of hydrogen, alkyl or substituted
- 15           alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, aryl or substituted aryl, arylalkyl or substituted arylalkyl, alkoxy and hydroxyl; and
- 20            $R_8'$  is selected from the group consisting of hydrogen, a bond, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, aryl or substituted aryl, arylalkyl or
- 25           substituted arylalkyl, alkoxy and hydroxyl, or  $R_8$  and  $R_8'$  together form a carbonyl,
- including all prodrug, stereoisomers and pharmaceutically acceptable salts thereof.
- 30           25. A pharmaceutical composition which functions as a selective agonist of the thyroid hormone receptor-beta comprising a compound as defined in claim 1.

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
20 November 2003 (20.11.2003)

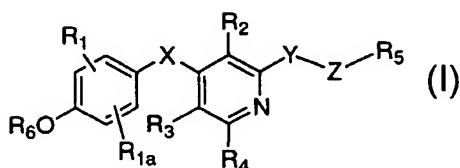
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(10) International Publication Number  
**WO 2003/094845 A3**

- (51) International Patent Classification<sup>7</sup>: **C07D 213/30**, 213/32, 213/36, 213/55, A61K 31/44
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- (22) International Filing Date: **7 May 2003 (07.05.2003)**
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- (30) Priority Data: **60/378,497** **8 May 2002 (08.05.2002)** **US**
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- (72) Inventors; and
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- (74) Agents: **O'BRIEN, Maureen et al.**; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).
- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
- with international search report
  - before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- (88) Date of publication of the international search report: **4 March 2004**

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PYRIDINE-BASED THYROID RECEPTOR LIGANDS



(57) Abstract: Novel pyridine-based thyroid receptor ligands are provided which have the general formula (I) wherein: X is oxygen (-O-), sulfur (-S-), sulfoxide (-S(O)-), sulfonyl (-SO<sub>2</sub>-), CR<sub>8</sub>R<sub>8</sub>' or NR<sub>8</sub>; Y is -NR<sub>8</sub>, oxygen (-O-), -CH<sub>2</sub>- or sulfur (-S-); Z is a bond or substituted or unsubstituted C<sub>1-4</sub> alkyl; and wherein the substituents are as described herein. In addition, a method is provided for preventing, inhibiting or treating diseases or disorders associated with metabolism dysfunction or

which are dependent upon the expression of a T<sub>3</sub> regulated gene, wherein a compound as described above is administered in a therapeutically effective amount.



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/14222

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : CO7D 213/30, 213/32, 213/36, 213/55; A61K 31/44

US CL : 546/22, 290, 304, 329, 339; 514/ 345, 349, 352

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/22, 290, 304, 329, 339; 514/ 345, 349, 352

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
STN.Registry, Caplus, Uspatful,

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6534522 B2 (BIGGE et al ) 18 MARCH 2003 (18.03.2003), column 45 line 45	1-25
A	US 6221911 B1 (LAVIN et al ) 04 April 2001 (04.04.2001) Column 16 claim 2.	1-25

<input type="checkbox"/> Further documents are listed in the continuation of Box C.		<input type="checkbox"/> See patent family annex.	
<p>* Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier application or patent published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>		<p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>	
<p>Date of the actual completion of the international search</p> <p>13 November 2003 (13.11.2003)</p>		<p>Date of mailing of the international search report</p> <p>22 DEC 2003</p>	
<p>Name and mailing address of the ISA/US</p> <p>Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230</p>		<p>Authorized officer</p> <p>Alan Rotman <i>Janice Ford</i> Telephone No. 703-308-1235 <i>for</i></p>	

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US03/14222

### Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

### Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

PCT/US03/14222

### BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.  
Group I, claim(s) 1-25 In part , drawn to compounds, pharmaceuticals and method of treating using these compounds wherein X and Y are both Oxygen.

Group II, claim(s) 1-25 in part , drawn to compounds, pharmaceuticals and method of treating using these compounds wherein X is oxygen and Y is NR8

Group III, claim(s) 1-25 in part , drawn to compounds, pharmaceuticals and method of treating using these compounds wherein X is Oxygen and Y is S or CH2.

Group IV, claim(s) 1-25 in part , drawn to compounds, pharmaceuticals and method of treating using these compounds wherein X is S and Y is O, NR8 , S or CH2.

Group V, claim(s) 1-25 in part , drawn to compounds, pharmaceuticals and method of treating using these compounds wherein X is CR8R8' and Y is O, NR8 , S or CH2

(f) "Markush Practice." The situation involving the so-called "Markush practice" wherein a single claim defines alternatives (chemical or non-chemical) is also governed by Rule 13.2. In this special situation, the requirement of a technical interrelationship and the same or corresponding special technical features as defined in Rule 13.2, shall be considered to be met when the alternatives are of a similar nature.

(i) When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

(A) all alternatives have a common property or activity, **and**

(B)(1) a common structure is present, i.e., a significant structural element is shared by all of the alternatives, or

(B)(2) in cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

(ii) In paragraph (f)(i)(B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of the existing prior art. The structural element may be a single component or a combination of individual components linked together. The different X and Y substituents have so many permutations and combinations, they have different bonding and properties, and have achieved a different status in the art. The terms X and Y, are so broad in scope that a prior art reference anticipating the claims with respect to one member under 35 USC 102(b) would not render obvious the same claims under 35 USC 103a with respect to another member.

Also when a preliminary search was done on the core it gave numerous iterations indicating that applicants core is not the applicants contribution over the prior art, and does not constitutes a structurally distinctive portion in view of the existing prior art.

Thus Lack of Unity is proper.